REMARKS

Applicants have canceled claims 48-54 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application. Applicants thank the Examiner for his review of the pending application and Applicants' submission mailed on February 20, 2007. For the reasons below, Applicants respectfully traverse the pending rejections.

Rejection Under 35 U.S.C. §101

The Examiner maintains his rejection of the pending claims under 35 U.S.C. § 101 as lacking utility. The Examiner makes the following arguments in support of his rejection:

1. Gene expression data does not support utility for the claimed polypeptide because "Abundant art supports the absence of a necessary relationship between mRNA and protein," and "Protein and DNA Microarray data shows no necessary correlation between mRNA overexpression and protein expression." *Office Action* at 3-10 (emphasis added). The Examiner cites as support, Meric, Gokman-Polar, Pennica, Orntoft, Czupalla, Kwong, Chen, Conrad, Ginestier, Anderson, Washburn, Lee, and Provenzani for support.

2. The Examiner has attacked the sufficiency of the gene expression data, stating that "there is no evidence that the overexpression effect was statistically significant" or "reproducible," that "many genes are irrelevant in gene microarray assays," and that "matched tissue samples were not used for controls." *Office Action* at 10-12. The Examiner cites Li, Ding, and Sawiris for support.

3. Finally, the Examiner argues that "[s]pecific data shows that Pro539 is NOT overexpressed in lung tumors." *Office Action* at 13-15.

The Board of Patent Appeals and Interferences has Affirmed Applicants' assertion that overexpression of mRNA in tumors is sufficient to establish a specific and substantial utility for the encoded polypeptide

In a non-precedential opinion involving many of the same inventors of the instant application, *Ex parte Goddard*, Appeal No. 2006-1469, the Board of Patent Appeals and

Interferences (Board of Appeals) held that microarray data demonstrating overexpression of a gene in tumors compared to non-cancerous controls is "sufficient to establish a specific and substantial utility for the polypeptide," even though there was no data regarding expression of the claimed polypeptide. *Ex parte Goddard* at 9 (opinion attached as Exhibit 1 for Examiner's convenience). In that appeal, the Board of Appeals reversed the examiner's §101 utility rejection, rejecting many of the arguments made by the Examiner in the instant application. Of particular note, the Board of Appeals stated:

> The microarray data demonstrates that mRNA for the PRO1866 polypeptide (SEQ ID NO: 14) is overexpressed in colon tumor, prostate tumor, and lung tumor, as compared to universal normal control. Thus, the polypeptide of SEQ ID NO:14 has a significant and presently available benefit to the public as a tumor marker.
>
> We have considered the Examiner's assertions that microarray analysis measures mRNA levels, and not overexpression of the polypeptide of SEQ ID NO:14 itself. As demonstrated by the Polakis and Smith Declarations, however, there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that.
>
> Finally, the use of the PRO1866 polypeptide as a cancer marker is sufficient to demonstrate utility, and there is no requirement that a causative link between the polypeptide (or nucleic acid) of the present invention and colon, lung or prostate tumors be demonstrated. *Id.* at 9-10 (emphasis added).

Given the Board of Appeal's opinion in *Ex parte Goddard*, Applicants respectfully request that the Examiner reconsider his utility rejection, as Applicants have established that PRO539 mRNA is overexpressed in a significant number of lung tumors tested by Applicants, including a majority of squamous cell lung tumors. *See Smith Declaration* at ¶7. In addition, nearly all of the Examiner's arguments in support of his utility rejection have been addressed and rejected by the Board of Appeals.

The Board of Appeals has rejected the Examiner's argument that there is no relationship between mRNA and protein expression

The Examiner has argued that the claimed polypeptide lacks utility because there is "no necessary correlation between mRNA overexpression and protein expression." *Office Action* at 6 (emphasis added). In the Examiner's Answer brief in *Ex parte Goddard*, the examiner made similar arguments:

> [T]he microarray analysis merely measures the mRNA level; it does not measure the over-expression of the polypeptide of SEQ ID NO: 14. There is no evidence regarding whether the level of PRO1866 polypeptide of SEQ ID NO: 14 or, even more broadly, its variants significantly increased in colon, lung or prostate tumor samples in comparison with the normal control. *Examiner's Answer Brief* at 16 (hereinafter "Answer Brief;" attached as Exhibit 2 for Examiner's convenience) (emphasis added).

> Appellant's reasoning is flawed logically and does not account for a gap between a gene expression level and a protein level. The molecule detected by the microarray was one specific mRNA that is complementary to the nucleic acid of SEQ ID NO: 13 and encodes the polypeptide of SEQ ID NO: 14, not the polypeptide of SEQ ID NO: 14, not the variants of the polypeptide of SEQ ID NO: 14. There is no correlative link established between the level of gene expression and the level of the protein in general (see below for details). *Id.* at 18 (emphasis added).

> Clearly, Appellant's argument that a positive correlation exists between mRNA and protein is not true. ...Haynes et al. conclude "The multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (bottom of left column of page 1870). Accordingly, the limited disclosure in the instant case does not meet the legal standard for a specific and substantial utility required under 35 U.S.C.§ 101. *Id.* at 24 (emphasis added).

> There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoding polypeptide. In fact, the art teaches the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (Haynes et al., Electrophoresis, 19:1862-1871, 1998; see, left column of page 1863; Figure 1). *Id.* at 30 (emphasis added).

In response to the examiner's arguments in *Ex parte Goddard*, the Board of Appeals **rejected** the argument that mRNA expression levels do not reflect protein expression levels:

> We have considered the Examiner's assertions that microarray analysis measures mRNA levels, and not overexpression of the polypeptide of SEQ ID NO:14 itself. As demonstrated by the Polakis and Smith Declarations, however, there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that. *Ex parte Goddard* at 9 (emphasis added).

The same facts are present in the instant case. Applicants have made of record a declaration of Dr. Polakis, where he makes the same statements relied on by the Board of

Appeals. Similarly, in the declaration by the same Dr. Smith, previously made of record in the instant case, she states:

> It is well-established in the art that overexpression of the mRNA for a gene is likely to lead to overexpression of the corresponding protein. ... Given the known correlation between overexpression of a gene and the corresponding overexpression of the encoded protein, it is very likely that a similar number of lung tumors will overexpress the PRO539 protein, while very few normal lung tissue samples likely will. *Smith Declaration* at ¶¶6-7 (emphasis added).

In addition to the declarations by Drs. Polakis and Smith, Applicants have made of record the declaration of J. Christopher Grimaldi, who states: "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed, as evidenced by an increased production of mRNA, the gene product or polypeptide will also be over-expressed." *Grimaldi Declaration* at ¶5. Likewise, the declaration of Dr. Scott, an independent expert states: "[G]enerally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. ...[I]t has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue." *Scott Declaration* at ¶10. These statements are supported by the numerous references made of record by Applicants (Exhibits 1, 2, 4, 5, several of the references submitted as Exhibit 7, and Exhibits 11-20, submitted with Applicants' response mailed February 20, 2007.) In sum, Applicants have made of record the opinions of the same experts relied on by the Board of Appeals in *Ex parte Goddard*, as well as two additional experts and numerous supporting references.

Thus, as in *Ex parte Goddard*, Applicants have established that "there is a strong correlation between mRNA levels and protein expression." *Ex parte Goddard* at 9. And, as in *Ex parte Goddard*, "the Examiner has not presented any evidence specific to the PRO[] **polypeptide** to refute that." *Id.* (emphasis added). Given these facts, Applicants respectfully request that the Examiner reconsider his utility rejection, as the Board of Appeals has rejected his position that evidence of polypeptide overexpression is required – overexpression of the mRNA is sufficient to establish the utility of the encoded protein.

The Board of Appeals has rejected the Examiner's argument that the overexpression data needs to be statistically significant and relative to tissue matched control, or is otherwise "irrelevant"

The Examiner in the instant case has argued that the data showing amplification and overexpression of PRO539 nucleic acids are insufficient because there is no evidence that they are statistically significant, reproducible, not the result of nonspecific effects or a single tumor sample, or simply biologically irrelevant. *Office Action* at 10-12. In addition, the Examiner argues that tissue matched controls are required. *Id.* at 12. In the Examiner's Answer Brief in *Ex parte Goddard*, the examiner made these same arguments regarding the sufficiency of Applicants' data:

> There is no statistical analysis or validation analysis of the expression data. Numerous questions remain to be answered: such as how many tumor samples and normal control samples were used in the study? How were the normal control samples pooled? What types of colon, lung or prostate tumor samples were utilized in the assay (there are different types of lung tumors, for example)? What were the actual level or relative degree of expression of the protein or the nucleic acid encoding the polypeptide in the universal control versus the tumor samples? How to distinguish a truly positive hybridization signal from a false one? How many fold difference in the expression level between a tumor sample and a normal control was considered as being significant? Without such critical information, how would one of skill in the art be able to quantitatively compare the level of PRO1866 expression in a tumor sample to a normal control sample and to detect a relative difference in the level of PRO1866 expression between the tumor and normal samples? *Answer Brief* at 19 (emphasis added).
>
> [S]tatistical analysis and validation analysis are needed to establish a marker for diagnosis of a certain type of tumor, for example, lung adenocarcinomas. A sufficient sample size (i.e., number of tumor samples and healthy control samples) is required for assessment of the difference in the expression level of a gene or protein at a given significance level (e.g., P<O.01). Without such an analysis, one of skill in the art would not be able to judge whether a nucleic acid or a protein can be practically used as a diagnostic marker for a specific type of tumor. *Id.* at 22 (emphasis added).
>
> Hu et al. clearly states: "it is not uncommon to see expression changes in microarray experiment as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful" (bottom of right column of page 411). Hu et al. further states: "in any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study" (1st paragraph of left column of page 405).

> Accordingly, in view of the limited disclosure in the instant case--lack of disclosure of the "cut-off ratio" that was used to determine whether a hybridization signal was significant, lack of the statistical analysis, lack of the validation of universal normal control, and lack of establishment of a correlative link between gene expression and protein level or a causal link between gene expression and colon, lung or prostate tumours, the teachings of Hu et al. support the Examiner's position that further research is needed to reasonably identify or confirm a specific and substantial utility for the instantly claimed polypeptide of SEQ ID NO: 14 and its variants. *Id.* at 27 (emphasis added).
>
> Furthermore, the specification provides no information regarding the specific degrees of the increase in mRNA level or protein levels of PRO1866 in tumor tissues relative to corresponding normal tissues. There is no statistical analysis of the expression data. For example, there is no disclosure of the number of tumor samples and control samples that were analyzed, which is clearly required for the establishment of a reliable diagnostic marker for colon, lung or prostate tumors. *Id.* at 30-31 (emphasis added).

From the above quotes, it is apparent that the Board of Appeals was presented with the same arguments in *Ex parte Goddard* that the Examiner is making in the instant case regarding the sufficiency of the nucleic acid expression data. The Board of Appeals **rejected** the examiner's assertion that the data were irrelevant or insufficient in any way, stating that the microarray data were "sufficient to establish a specific and substantial utility" for the claimed polypeptides. *Ex parte Goddard* at 9. Given the Board of Appeal's rejection of the examiner's attempts to heighten the utility standard in *Ex parte Goddard*, Applicants respectfully request that the Examiner withdraw his utility rejection of the instant claims based on the same flawed reasons.

The Examiner argues that "the art supports the conclusion that many genes are irrelevant in gene microarray assays." *Office Action* at 11. Relying on Li, Ding, and Sawiris, the Examiner concludes that "the overwhelming state of the art supports the position that many genes are irrelevant, that genes whose expression does not change are noise, and that these irrelevant genes are so insignificant that ideally they are not placed on the arrays or used at all. The current gene, Pro539, is such a gene." *Id.* The Examiner concludes given "the absence of any direct association with Pro539 and lung tumors, this gene represents noise. ... Therefore, genes such as Pro539, lack substantial utility as useful on gene expression arrays." *Id.*

This argument is unpersuasive for several reasons. First, the Board of Appeals rejected a similar argument by the examiner in *Ex parte Goddard*, who argued that "Hu et al. further states: 'in any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study.'" *Answer Brief* at 27 (emphasis added). The additional references cited by the Examiner in the instant case do not provide any additional reason for the Board of Appeals to reach a different conclusion here (see discussion below).

Second, as discussed in Applicants' previous response, the Examiner has already accepted that the PRO539 gene has utility as a diagnostic tool in a related application. It is inconsistent and arbitrary for the Examiner to now argue the exact opposite position in the instant case. While decisions of administrative agencies like the PTO are given deference by the courts, decisions which are arbitrary and capricious will be overturned.

As for the three references cited by the Examiner, they do not support a rejection of the instant claims. Applicants do not dispute that genes can be irrelevant when it comes to use in gene microarrays. However, the cited references do not support the Examiner's conclusion that a gene which is significantly amplified or overexpressed in certain cancer cells, such as the gene which encodes PRO539, is not useful in a gene microarray. The cited statements from Li, that there are important and irrelevant genes and that it is useful to remove the irrelevant genes from microarrays, are statements of the obvious, and offer no support for an argument that the gene encoding PRO539 is one of the irrelevant genes. To the contrary, Li goes on to analyze an example of a microarray used to distinguish cancerous tissue from normal tissue. (Li at 543.) The authors state that in making such a distinction, they are most interested in genes that are expressed higher in cancerous tissues than in normal tissues. (*Id.*) Thus, Li teaches that the gene encoding PRO539 is an example of a gene that would be of interest.

Likewise, the Examiner cites Ding for the proposition that genes without changes in expression profiling should be discarded as irrelevant. Regardless of the merits of the novel method disclosed in Ding, PRO539 does show a change in expression profile between lung and colon tumors and normal tissue. Thus, nothing in Ding supports the Examiner's conclusion that a gene which is significantly overexpressed in certain cancer cells, such as the gene encoding PRO539, is not useful in a gene microarray.

Finally, the Examiner cites Sawiris for the obvious statement that "[o]ne of the advantages of specialized arrays is that they do not include irrelevant genes that may contribute to noise during data analysis." What the Examiner fails to note is that the genes that were chosen for inclusion in the specialized chip were those that were either overexpressed or underexpressed in ovarian cancer. (Sawiris at 2923, second column.) Thus, contrary to the Examiner's assertions, the gene encoding PRO539 is useful for microarrays since it is overexpressed in certain colon and lung tumors.

Therefore, the three references cited do not support the Examiner's rejection of the asserted utility of using the gene encoding PRO539 as a diagnostic agent for cancer. While the Examiner's statement that the prior art supports the conclusion that there are many irrelevant genes is not disputed, none of the references support the conclusion that the gene encoding PRO539 is one of those irrelevant genes when it comes to a diagnostic tool for cancer, particularly colon and lung cancer. To the contrary, the references indicate that the relevant genes are those that are overexpressed or underexpressed in the cancer of interest, genes like the one which encodes PRO539. Thus Applicants submit that the Examiner has failed to offer any support for his conclusion that the gene encoding PRO539 represents "noise" and is not useful as a cancer diagnostic tool.

In sum, the Board of Appeals has rejected the same arguments in *Ex parte Goddard*, and will do the same in the instant case. Applicants therefore request that the Examiner withdraw his rejection of the pending claims.

Applicants' evidence establishes that the PRO539 mRNA is overexpressed in a significant portion of lung tumors tested, and a majority of squamous cell lung tumors tested

The only one of the three arguments made by the Examiner in the instant case that was not presented to the Board of Appeals and subsequently rejected in *Ex parte Goddard*, is the Examiner's argument that "[s]pecific data shows that Pro539 is NOT overexpressed in lung tumors." *Office Action* at 13-15. To support this statement, the Examiner cites two datasets for Kif7 gene expression from the NCBI website. The first is from a study titled "Lung neuroendocrine tumor classification," and the second is from a study titled "Colorectal carcinoma subtype with microsatellite instability." The Examiner characterizes the first study as finding "no

correlation whatsoever between expression and cancer," and the second study as appearing to show "no relationship with cancer."

Applicants note that in the second study, all of the samples tested were tumor samples. Because there are no normal controls of any kind, it is impossible to say whether Kif7 is overexpressed in colorectal tumors relative to normal tissue. Therefore, these data provide no support for the Examiner's position.

While the first study appears to show overexpression of Kif7 in only a few (four) tumor samples relative to controls, none of the control samples show overexpression of Kif7. This is similar to Applicants' data previously submitted with the declaration of Dr. Smith. Dr. Smith states in her declaration that:

> [T]he gene encoding PRO539 (DNA47465) is significantly overexpressed in eight of the twenty-six lung tumor samples tested compared to the normal lung tissue controls. That is the equivalent of nearly one in every three samples (31%). In addition, four out of five squamous cell lung carcinomas (80%) are significantly overexpressed (shown in bold). In contrast, only one of the seven individual normal lung tissue samples shows significant overexpression of the PRO539 gene (14%). *Smith Declaration* at ¶5.

Given the overexpression of PRO539 in a significant portion of lung tumors tested, including a majority of squamous cell tumors, and only a single normal tissue showing overexpression, Dr. Smith concludes that PRO539 nucleic acids and polypeptides are useful as diagnostic tools:

> Given the known correlation between overexpression of a gene and the corresponding overexpression of the encoded protein, it is very likely that a similar number of lung tumors will overexpress the PRO539 protein, while very few normal lung tissue samples likely will. Together with the data reported in Example 16 that the gene encoding PRO539 is amplified in some lung tumors, including squamous cell lung carcinoma, the results reported in Exhibit B indicate that the PRO539 gene and protein, as well as antibodies to the encoded protein, can be used to differentiate some cancerous lung tissue, particularly squamous cell carcinoma, from normal lung tissue. Because not all lung tumors show overexpression of PRO539, it cannot be used to exclude a sample being tested as non-cancerous. However, the PRO539 gene, protein, and corresponding antibodies are useful as a diagnostic tool for lung cancer, particularly squamous cell carcinoma, since a very high percentage of squamous cell lung carcinomas overexpress the gene and most likely the encoded protein, while very few normal lung samples do. *Smith Declaration* at ¶7 (emphasis added).

Nothing in the results of the "Lung neuroendocrine tumor classification" study are contrary to Dr. Smith's opinion or accompanying data. Therefore, even if the Examiner's characterization of the Kif7 lung tumor study is correct, it is not contrary to Applicants' own data and does not provide a basis to reject the conclusions of Dr. Smith. Because this argument does not support the Examiner's utility rejection, and the Examiner's other arguments have been presented to the Board of Appeals and rejected, Applicants respectfully request that the Examiner withdraw his utility rejection of the pending claims.

The Examiner's cited references are Not Relevant to determining whether a change in mRNA level for a particular gene leads to a corresponding change in the level of the encoded protein

As noted above, the Board of Appeals has rejected the Examiner's position that overexpression of mRNA in tumors is not sufficient to provide utility for the claimed polypeptide. However, in the interest of thoroughness, Applicants respond below to the Examiner's argument that "[n]ine out of ten recent microarray papers show discordant protein and mRNA expression data." *Office Action* at 6-10.

As an initial matter, Applicants reiterate that Applicants' asserted utility does not require that all changes in protein levels result from changes in mRNA level. Applicants' assert that, as a general rule, gene amplification leads to overexpression of the mRNA and encoded protein. The fact that protein levels can change in the absence of gene amplification or a change in mRNA is not relevant to Applicants' asserted utility – Applicants are not trying to determine or predict mRNA levels by examining changes in protein level.

The Examiner has yet to explain his continued reliance on data purportedly showing protein changes in the absence of mRNA changes. His only response is that "[t]he point of the citation was that there was no necessary correlation." *Office Action* at 37. This is not an explanation as to how this data is in any way relevant. There could be an absolute, perfect and necessary correlation between increased mRNA expression leading to increased protein expression, but still be cases where protein expression changes in the absence of a change in mRNA expression. This is because a change in mRNA expression can be a sufficient cause (i.e., it always causes), but not necessary cause (i.e., other causes exist), of changes in protein

expression. The Examiner's statement requires further explanation as it is contrary to basic principles of cause and effect.

a. Czupalla et al.

The Examiner states that "[t]he data of Czupalla, which addresses 117 genes, shows that it is more likely than not in this data set that there is no correlation between mRNA expression and protein expression. This supports the conclusion that mRNA expression cannot be relied upon for enablement and utility of the protein since no necessary correlation exists." *Office Action* at 6-7 (emphasis added).

This argument fails for two reasons. First, as stated numerous times, a "necessary" correlation is not required for utility – a reasonable correlation is all that is required. The Examiner's failure to accept the proper standard in light of clear teaching from the Courts, and more recently the Board of Appeals in *Ex parte Goddard*, is baffling. Second, the Examiner's conclusion is not supported by Czupalla, which reports on changes in protein expression in osteoclastogenesis. As the Examiner notes, the authors report finding two groups of proteins: those where there is a change in mRNA with a corresponding change in protein, and those where there is a change in protein and no change in mRNA. As discussed above, and previously, Applicants are not concerned with predicting mRNA levels from changes in protein, and therefore a lack of correlation in the second group is irrelevant.

As for the first group, the authors report that "the first group comprises 47 genes for which differences in mRNA expression and in abundance of the corresponding protein spots on 2-D gels were consistently detected," listing genes "which are increased on the mRNA and protein level," as well as genes "for which mRNA and protein expression are downregulated." *Czupalla* at 3873, right column. The authors conclude by stating that "[t]hus, differential expression of many genes during osteoclastogenesis was confirmed by two complimentary techniques." *Id.* at paragraph bridging 3873-3874. Only three of the 47 genes from the first group are mentioned as having discordant mRNA and protein changes. *Id.* at 3874, right column, first paragraph. Apparently, the other 44 genes, or 94%, showing a change in mRNA had a corresponding change in protein. Therefore, rather than supporting a lack of correlation between changes in mRNA leading to changes in protein, Czupalla actually strongly supports Applicants' position, and the position adopted by the Board of Appeals.

b. Kwong et al.

The Examiner states that Kwong analyzed 47 genes in colorectal cancer, and that "Only 12 of 47 genes exhibited correlated expression at a significance level less than 0.05. Surprisingly, 13 genes had a negative correlation between mRNA and protein levels." *Office Action* at 7. The Examiner also relies on Kwong's statement that "correlation between protein and mRNA was also compared on a sample-by-sample basis. Of the 53 samples for which data was available, mRNA and protein levels were found to be correlated at a significance level of 0.05 in only 14 samples, while 14 mRNA and proteins were negatively correlated." *Id.* Based on Kwong, the Examiner concludes that "Kwong supports the conclusion that it is more likely than not that there is no correlation." *Id.*

The Examiner's reliance on Kwong is misplaced because neither portion of Kwong is contrary to Applicants' position that changes in mRNA expression levels lead to changes in protein expression levels. In the first portion of the paper quoted by the Examiner, the authors report that of 47 genes examined at the mRNA and protein level, only 12 exhibited a significant correlation between the two measures. This study is not applicable to Applicants' assertion because the authors were not comparing changes in mRNA against changes in protein levels. The correlation relied on by the Examiner is simply a plot of RNA level versus protein level for all of the samples where both RNA and protein was detected – the authors were not examining differential mRNA expression between normal and tumor tissue to see if there was a corresponding change in protein level. Of the 47 genes examined, only two are identified by the authors as having differentially expressed mRNA between the normal and tumor samples (PCNA and CKB; see Table 9, and compare to Tables 2, 3, 6 and 7, and text on page 146, right column, first paragraph), and both of these genes show a correlation (r=0.567 and 0.545) between mRNA and protein. As for the other 45 genes in Table 9, there is no indication that mRNA levels are differentially expressed between normal and tumor samples, and therefore they say nothing about whether changes in mRNA lead to changes in protein expression.

It is clear that the authors were not looking at differentially expressed genes in the section of the paper discussed above from the fact that under the heading "Differential expression of mRNA and proteins," the authors discuss the mRNA and proteins that were differentially expressed between tumor and normal tissue. The authors state that "cross-validation between

RNA and protein expression levels on a gene-by-gene basis was not performed since the overlap between the identified proteins and the probes on the cDNA microarray was very limited." *Kwong* at 146, right column, second paragraph (emphasis added). Because an analysis of the differentially expressed mRNAs and proteins was not conducted, Kwong does not address the issue of whether changes in mRNA lead to changes in protein.

As for the second portion of Kwong, where the authors looked at mRNA and protein levels on a sample-by-sample basis, this is also irrelevant to the issue of whether a change in mRNA level leads to a change in protein level. In a sample-by-sample comparison, the authors are looking for a correlation between the level of mRNA and corresponding protein by plotting a single measurement of mRNA level vs. protein level for the 47 different genes in a single sample. The only way that such a plot would result in a significant correlation is if there exists a ratio between mRNA levels and protein levels that is the same across all genes, *i.e.*, that for every X copies of an mRNA, there are Y copies of the encoded protein, such that the ratio of X:Y is constant across all genes. The data from Kwong indicates that only 14 of 53 samples showed a positive correlation in this analysis. All this proves is that in most samples examined, the ratio of mRNA:protein level varies for different genes, *i.e.* no common ratio exists. This does not mean that increasing or decreasing mRNA levels for a particular gene will not result in an increase or decrease in protein level.

Applicants' asserted utility does not require knowledge of, or even the existence of, a common ratio between mRNA levels and protein levels across different genes. Nor do Applicants' assertions require calculation of protein levels based on measured mRNA levels. Applicants are not relying on a single measure of mRNA for a particular gene and then attempting to calculate protein levels based on a common global ratio between mRNA and protein levels. Instead, Applicants are relying on differential mRNA expression, where mRNA levels are measured in two different conditions, i.e. tumor and normal. Applicants assert that a change in mRNA expression level for a particular gene typically leads to a corresponding change in the expression level of the encoded protein. The Kwong reference is applicable to only a completely unrelated issue – whether a single measure of mRNA levels can be used to predict protein levels – and therefore, this reference has no bearing on Applicants' assertions.

Applicants note that this is the same kind of study, i.e., looking for a global mRNA:protein ratio across genes, that was conducted by Haynes, *et al.* (Electrophoresis, 19(11):1862-71 (1998)). It is the Haynes reference that was relied on by the examiner in *Ex parte Goddard* to support the examiner's argument that mRNA levels cannot be used to predict protein levels:

> Clearly, Appellant's argument that a positive correlation exists between mRNA and protein is not true. ...Haynes et al. conclude "The multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (bottom of left column of page 1870). Accordingly, the limited disclosure in the instant case does not meet the legal standard for a specific and substantial utility required under 35 U.S.C.§ 101. *Answer Brief* at 24 (emphasis added).

> There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoding polypeptide. In fact, the art teaches the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (Haynes et al., Electrophoresis, 19:1862-1871, 1998; see, left column of page 1863; Figure 1). *Id.* at 30 (emphasis added).

The Board of Appeals did not find the examiner's arguments based on Haynes *et al.* persuasive, as the Board of Appeals reversed the examiner's utility rejection. Applicants submit that for the same reasons, the Board of Appeals will find Kwong and similar references unpersuasive.

c. Chen et al.

The next reference relied on by the Examiner is by Chen *et al.* The Examiner quotes Chen as stating: "By comparing the mRNA and protein expression levels within the same tumor samples, we found that 17% (28/165) of the protein spots (21/98 genes) show a statistically significant correlation between mRNA and protein." *Office Action* at 7. The Examiner also relies on Chen's statement that: "The majority of protein isoforms, however, did not correlate with mRNA levels and thus their expression is regulated by other mechanisms. We also observed a subset of proteins that demonstrated a negative correlation with the mRNA expression values." *Id.*

As an initial matter, it is important to note that a portion of Chen apparently not relied on by the Examiner is irrelevant to Appellants' assertion that changes in the level of mRNA lead to changes in the level of the encoded polypeptide. In one experiment similar to that of Kwong, Chen examined the relationship between mRNA and the corresponding protein abundance by calculating the average mRNA and protein level of all the samples for each gene or protein, and then looked for a correlation across different genes. This is similar to the sample-by-sample comparison done by Kwong and Haynes, only the data were averaged across all samples. Based on these data, Chen reported that "no significant correlation between mRNA and protein expression was found ($r = -0.025$) if the average levels of mRNA or protein among all samples were applied across the 165 protein spots (98 genes)." *Chen* at Abstract. This measurement of a correlation across <u>different</u> genes is not relevant to Appellants' asserted utility for the same reasons discussed above with respect to the Kwong *et al.* reference – it merely shows that in the samples tested, there is no common or global ratio of mRNA:protein that applies across all genes.

Chen also looked at the level of mRNA of 98 individual genes and their corresponding proteins by plotting the data from across the samples. Chen reports that 17% (28 of 165) of the protein spots, or 21.4% (21 of 98) of the genes, showed a statistically significant correlation between protein and mRNA expression. *Chen* at Abstract. It is these results that the Examiner relies on for support.

However, read in its entirety, Chen provides scant evidence to counter Applicants' assertions because Chen provides little insight into the relationship between changes in mRNA levels and changes in the corresponding protein levels for mRNA that is differentially expressed in tumor cells relative to normal cells.

Applicants have asserted that <u>changes</u> in mRNA levels will correspond with measurable changes in polypeptide expression. Like Kwong, Chen did not examine differential mRNA expression between normal and cancer samples, and then attempt to determine if the differential mRNA expression results in differential protein expression. Stated differently, if there is no substantial change in mRNA levels for a particular gene, one cannot measure a correlation between changes in mRNA and changes in the encoded protein for that gene. Therefore, one must know if the individual genes studied by Chen were differentially expressed to know if the

observed lack of correlation has any relevance to Applicants' assertions of a general correlation between changes in mRNA and protein.

Importantly, unlike Applicants, Chen did not examine differences in mRNA between tumor and normal tissue where one would expect to find substantial changes in the level of mRNA for certain genes. Instead, Chen merely selected proteins whose identity could be determined regardless of any changes in expression level. *Chen* at 306, right column. Therefore, it is not known if there was any substantial difference in mRNA levels for the various studied genes across samples – in short, with the exception of the genes in Figures 2A-2C, where a correlation is observed, it is not known if the genes examined were differentially expressed. Also of significance for Applicants' asserted utility is the fact that Chen did not attempt to examine any differential expression between the cancerous lung samples and the non-cancerous lung samples – Chen did not distinguish between cancer and normal samples in their analysis. In the absence of substantial differential expression, no correlation would be observed. As discussed above with respect to Kwong, because it is not known if there was a change in the level of mRNA for the genes studied by Chen, *i.e.* whether they were differentially expressed, the lack of an observed correlation cannot be used to counter Applicants' assertion.

In sum, the only data reported by Chen which shows substantial changes in the expression of mRNA, Figures 2A-C, supports Applicants' assertion that substantial changes in mRNA levels will correspond to substantial changes in polypeptide expression since a correlation was observed. As for the lack of an observed correlation between mRNA levels and protein levels for other genes reported by Chen, no conclusion can be drawn since there is no indication the genes are differentially expressed. Thus, Chen's results do not refute Applicants' position. If anything, Chen supports Applicants' position that a significant correlation between changes in mRNA and protein levels exists for changes in mRNA levels.

d. Conrad et al.

The Examiner relies on Conrad, asserting that comparing the abundance of protein to nucleic acid microarray for proteins, Conrad reported "There is little correlation between RNA and protein abundance identified and predicted by cICAT." *Office Action* at 8.

The Examiner's reliance on Conrad is misplaced for the same reason that the second portion of Kwong and the reference by Haynes is not relevant to Applicants' assertion. Conrad

reports on a combined proteome and microarray investigation of pre-osteoblasts stimulated with inorganic phosphate, examining the correlation between mRNA and protein levels across ~1900 different genes. However, like Kwong and Haynes, the authors of Conrad plotted a single time point for mRNA against a single time point for protein expression, looking for a correlation across the ~1900 genes. The only way this analysis will result in a significant correlation is if the ratio of mRNA:protein is constant across all ~1900 genes. Whether genes share a common mRNA:protein ratio or not is irrelevant because this type of experiment cannot address whether differential mRNA expression for a single gene generally results in differential protein expression for the corresponding protein – the two issues are independent of each other.

e. Ginestier et al.

The Examiner also relies on Ginestier, stating that table 4 teaches that only 5 of 15 genes showed concordance, and that the authors report that "For a category of molecules we found important differences between RNA and protein expression levels." *Office Action* at 8.

The Ginestier reference is difficult to interpret given the way the mRNA and protein samples were analyzed. The authors examined the level of mRNA and protein expression for 15 genes in 55 breast tumor samples. The authors then classified the protein and mRNA expression level for a particular gene in each sample as being either a class 1 (low), class 2 (mid), or class 3 (high). A contingency table analysis was then used to analyze the relationship between protein and mRNA expression for each gene. The authors report that only 5 of the 15 genes showed a significant relationship.

However, this analysis ignores the fact that in many cases, a relationship was not found because there were more samples with a "high" (class 3) protein expression level than there were samples with a "high" (class 3) mRNA level. For example, FGFR1 mRNA has 45 "low" (class 1), 10 "mid" (class 2), and 0 "high" (class 3) samples compared to FGFR1 protein which has 20 "low" (class 1), 20 "mid" (class 2), and 15 "high" (class 3) samples. *Ginestier* at Table 4. This is not contrary to Applicants' assertion, as Applicants are not arguing that "high" protein levels are always and only due to "high" mRNA expression. Applicants' assertion is that increasing mRNA levels lead to increasing protein levels, not the other way around. Thus, a lack of concordance because there are more "high" or "mid" protein samples than there are "high" or "mid" mRNA samples for a particular gene is not contrary to Applicants' assertion.

In addition, the assignment of the protein and mRNA expression levels to class 1, 2, or 3 was arbitrary, and influences whether a relationship is seen or not (for example, for some molecules, protein expression characterized as "strong" (S) in Table 3 is classified as class 3 (high) in Table 4 (e.g., BCL2) while for other molecules "strong" (S) protein expression is classified as class 2 (med) in Table 4 (e.g., Ki67)). These flaws, combined with the fact that Conrad was not looking at differential mRNA expression (*i.e.* a change in mRNA between condition X and condition Y), make Conrad of little value in assessing whether one of skill in the art would believe Applicants' assertions regarding differential mRNA expression leading to differential protein expression.

f. Anderson and Seilhamer

The Examiner argues that: "Anderson et al shows that for 19 proteins that were compared between 20 gel electrophoresis and mRNA analysis 'the correlation coefficient obtained over this set of data was 0.48. This number is intriguingly close to the middle position between a perfect correlation (1.0) and no correlation whatever (0.0).' In fact, the correlation is slightly closer to showing that there is no correlation whatsoever between protein and mRNA data." *Office Action* at 8.

Like the second portion of Kwong, Haynes, part of Chen, and Conrad, the Anderson paper is irrelevant because the authors examined the correlation between mRNA and protein across different genes – this is a search for a common global ratio of mRNA:protein. Applicants are asserting that if gene X is increased in cancer tissue relative to normal tissue, then protein X will be increased in cancer tissue relative to normal tissue. The truth of that assertion does not depend on a common global ratio of mRNA:protein across different genes.

To exemplify the difference between these references and Applicants' asserted utilities, Applicants offer the following illustration and analogy with the understanding that like all illustrations and analogies, they are not perfect and therefore do not represent any admissions or binding statements regarding Applicants' disclosure or invention.

Haynes, Kwong, Chen, Conrad and Anderson discuss whether there is a correlation between a single measure of mRNA and protein level globally, *i.e.* across different genes at a given time. This is equivalent to conducting a hypothetical Experiment 1, where a particular cell type has 100 copies of mRNA for gene X, 200 copies of mRNA for gene Y, and 400 copies of

mRNA for gene Z. If there is a common global ratio of mRNA:protein such that there is a correlation between mRNA levels and protein levels across genes, the relative amount of proteins X:Y:Z would be approximately 1:2:4 since this is the relative amount of their respective mRNAs. This is essentially what the cited references examined.

In contrast, Applicants are relying on a correlation between changes in mRNA level for a particular gene leading to a corresponding change in the level of the encoded protein when comparing tissues at two different times or conditions. For example, in hypothetical Experiment 2, if gene X has 100 copies of mRNA per cell in condition A (*e.g.* normal), and 200 copies of mRNA for gene X in condition B (*e.g.* tumor), the amount of protein X in condition A would be smaller than the amount of protein X in condition B, for example, having a ratio of 1:2, such that there is a correlation between the difference in the level of mRNA and the difference in the level of protein for a particular gene.

By relying on Kwong, Chen, Conrad and Anderson, the Examiner is apparently arguing that because there is no correlation between levels of mRNA and protein across genes in a particular sample, as illustrated by Experiment 1, one of skill in the art would not expect an increase or decrease in the amount of mRNA for a particular gene to result in a corresponding change in the amount of the encoded protein, as illustrated in Experiment 2. This is simply wrong – there does not need to be a global ratio of mRNA:protein across genes for there to be a correlation in changes of mRNA and protein for a particular gene.

The findings of Anderson that different amounts of mRNA result in different amounts of protein when looking across genes in a sample is analogous to finding that on one gallon of gas, a hybrid car can travel 50 miles, an SUV can travel 20, but a large truck can only travel 5 miles. If gas were plotted against miles for a variety of automobiles, there would be no correlation between gas and miles. That is to say, there are many things which affect the fuel efficiency of an automobile. Based on these observations, one could conclude that given the lack of a global ratio of gas to miles, and the resulting lack of correlation between the amount of gas in an automobile and the distance it travels, one cannot predict how far an automobile will travel based on a single measure of the amount of gas in the tank – one could conclude that it is more likely than not that there is no correlation between gas and miles.

Even if true, the data and conclusions of Kwong, Chen, Conrad and Anderson, like Haynes, are irrelevant to Applicants' assertions. Regardless of the fact that there are numerous levels of control of protein expression, Applicants assert that, generally speaking, increasing the amount of mRNA for a particular gene will result in a corresponding increase in the amount of the encoded protein. This is analogous to increasing or decreasing the amount of gas in an automobile – it will travel farther if you add more gas, and not as far with less. The fact that there are many things which affect fuel efficiency and therefore you cannot predict how far an automobile will travel without knowing if it is a hybrid or a large truck is irrelevant – both a hybrid and a truck travel farther on more gas, and not as far on less. A lack of correlation between gas and miles when examined across different automobiles does not mean that generally speaking, increasing the amount of gas means the automobile will travel further – they are independent and unrelated questions. The Board of Appeals has acknowledged this fact in *Ex parte Goddard.*

Applicants emphasize, and the Examiner will recognize, that these are simplified illustrations to demonstrate the difference between the two issues being examined. However, these illustrations make clear that even if there is no correlation in the first experiment looking at levels of mRNA and protein across genes in a sample, there can still be a correlation between changes in mRNA and protein for a particular gene as examined in the second experiment.

g. Washburn et al.

The next reference cited by the Examiner is Washburn, which the Examiner asserts found a correlation of 0.45 when examining 678 loci. *Office Action* at 8. The Examiner concludes that this is closer to the absence of a correlation than to a positive correlation. *Id.*

The authors of Washburn conducted an experiment which more directly addresses Applicants' assertion since they looked at the relationship between changes in mRNA and protein expression in yeast grown in minimal and rich media. The authors plotted the log of the ratio of mRNA expression in minimal and rich media against the log of the ratio of protein expression in minimal and rich media. The authors report a weak (0.45) correlation.

However, the authors note that "[a] majority of the data points deviating from the perfect positive correlation line shown fall on the y axis indicating that more loci had altered protein expression and unchanged mRNA expression than loci having altered mRNA expression and

unchanged protein expression." *Washburn* at 3109 column 1. In fact, looking at Figure 2, if the data points for loci where the mRNA levels did not change by at least two-fold are eliminated (*i.e.*, values between -1 and 1), it appears that there would be an excellent correlation between the changes in mRNA and the changes in protein. As Applicants' have previously stated, changes in protein level without changes in mRNA are not relevant to Applicants' assertion. The question is whether an increase in mRNA generally results in a change in protein. Based on the data in Washburn, the answer appears to be "yes." Thus, Washburn is not contrary to Applicants' assertion, but rather supports it.

h. Lee et al.

The next reference cited by the Examiner is Lee, which the Examiner quotes as stating: "Consistent with observation in other organisms, we observed no clear relationship between mRNA amplification and protein amplification factors for Escherichia coli." *Office Action* at 9.

Like the experiment by Washburn, the experiments of Lee are more relevant to Applicants' assertions than the experiments by Haynes, Kwong, Chen, Conrad and Anderson discussed above. This is because Lee plots the ratio of mRNA in two conditions against the ration of protein expression in the two conditions – Lee is attempting to examine changes in mRNA expression. However, as Figures 3 and 4 indicate, the conditions examined by Lee did not result in significant changes in mRNA. Instead, the vast majority of the data points have between 0.5 and 2 mRNA amplification factor, indicating that they had less than a two-fold change in mRNA level. Because the level of mRNA is not changing, there is no way of observing an affect on the level of protein expression. While Figure 3B does have a few data points that show greater than 2-fold changes in mRNA level, most of which do not show a corresponding change in protein level, this is hardly a "global comparison" as suggested by the Examiner. It is at best, a single study in which the authors demonstrate that under a minor environmental perturbation of *E. coli* by the addition of IPTG, approximately 17 genes showed a change in gene expression without an equivalent change in protein expression. It should not be given any special weight in considering Applicants' assertions, and must be considered along with the four expert declarations and dozens of references submitted by Applicants.

i. Provenzani et al.

The final reference cited by the Examiner is Provenzani, which the Examiner characterizes as a comparison of total mRNAs and polysomal mRNA, "which are the mRNAs which will undergo translation into protein. *Office Action* at 9. The Examiner quotes Provenzani as stating that "our analysis shows that 80% of the genes undergoing a gene expression change in the transition between SW480 and SW620 cells do it by varying their degree of polysomal loading, implying a dramatic subversion in the signaling control of translation and/or in the translational machinery itself." *Id.* (emphasis added). The Examiner concludes that Provenzani "supports the conclusion that up to 80% of genes will not show differential expression based upon mRNA level, but rather based on polysomal loading, so that mRNA level will not provide significant information regarding the utility, or lack thereof, for the protein." *Id.*

Applicants submit that the Examiner is again confusing cause and effect, and the difference between attempting to predict changes in mRNA levels from changes in protein levels, rather than trying to predict changes in protein levels based on changes in mRNA levels. Even if Provenzani is correct, and polysomal mRNA loading is an accurate indirect measure of protein levels, all that can be concluded from their statement is that 80% of proteins with changed expression levels do not rely on changes in total mRNA level. However, this does not mean that changes in total mRNA levels to not result in corresponding changes in protein levels – the issue at hand. If, as Applicants assert, there is generally a corresponding change in protein level when mRNA levels are changed, then one can predict changes in protein level from changes in mRNA level. The statement that 80% of genes studied by Provenzani do not rely on changes in total mRNA level, even if true, is not contrary to Applicants' assertions – changes in protein level in the absence of changes in mRNA level are not contrary to Applicants' assertions.

Conclusion – the Examiner's arguments are not sufficient to provide a basis for one of skill in the art to doubt Applicants' asserted utility

Applicants have shown that nearly all of the references relied on by the Examiner are either irrelevant, not contrary to Applicants' assertions, or actually support Applicants' position, not the Examiner's. Taken together, the Examiner's arguments are not sufficient to satisfy the burden to "provide[] evidence showing that one of ordinary skill in the art would reasonably

doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

Instead, considering all of the evidence of record, including four expert declarations, and dozens of supporting references, an unbiased observer would conclude that it is more likely than not that overexpression of PRO539 mRNA leads to overexpression of PRO539 protein, and therefore the claimed polypeptides have a specific and substantial utility. This is the conclusion that the Board of Patent Appeals and Interferences reached in a similar case: "We find that the microarray data [showing overexpression in certain tumors] is sufficient to establish a specific and substantial utility for the polypeptide." *Ex parte Goddard* at 9 (emphasis added). In light of the evidence of record and the proper legal standards established by the courts and adopted by the Board of Appeals in *Ex parte Goddard*, Applicants respectfully request that the Examiner withdraw the utility rejection of the pending claims.

Rejection under 35 U.S.C. §112 – Written Description

The Examiner has rejected pending Claims 48-54 under 35 U.S.C. §112, first paragraph, as lacking an adequate written description, stating that "there is no record of description which would demonstrate conception of any proteins other than those expressly disclosed which comprise SEQ ID NO:7." *Office Action* at 22. Applicants respectfully traverse for the reasons of record.

However, solely in the interest of advancing prosecution, Applicants have canceled claims 48-54, rendering this rejection moot.

Rejection under 35 U.S.C. §112 – Enablement

The Examiner has rejected claims 27-28, 32-34 and 48-54 under 35 U.S.C. §112, first paragraph, arguing that the claimed subject matter was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. *Office Action* at 22-36. The Examiner recites the factors for determining enablement from *In re Wands*, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988), relying to a large extent on the arguments made above in support of the rejection for lack of utility. Applicants have addressed each element of the Examiner's enablement rejection, either previously or above in the context of the utility rejection.

Applicants submit that pending claims 27-28, and 32-34 are enabled such that one of skill in the art could make and use the claimed polypeptides without undue experimentation. With respect to Claims 27-28 and 32-34, how to make the polypeptide of SEQ ID NO: 7 and the polypeptide encoded by the cDNA deposited under ATCC accession number 203661 is within the skill in the art. Thus, one of skill in the art would be able to make the claimed polypeptides without undue experimentation, and the Examiner has not made any arguments to the contrary.

As described above, Applicants assert that the claimed polypeptides are useful as diagnostic tools for cancer, particularly lung and colon cancer. This use is based on the disclosure that the PRO539 gene is amplified at least two-fold in a significant number of the lung and colon tumors tested, and microarray data showing that PRO539 mRNA is overexpressed in a significant portion of lung tumors. As detailed above, it is well-established that gene amplification is correlated with an overexpression of the corresponding mRNA and the encoded polypeptide, and thus it is more likely than not that the PRO539 polypeptide is overexpressed in lung and colon cancer. In addition, in *Ex parte Goddard*, the Board of Appeals has held that overexpression of the nucleic acid is sufficient to establish utility for the encoded polypeptide. Thus, based on the disclosure in the application, one of skill in the art would be able to use the claimed polypeptides as diagnostic tools to distinguish suspected lung and colon tumors from normal tissue without undue experimentation.

Because Applicants' specification teaches how to make and use the claimed subject matter, it must be taken as being in compliance with the enablement requirement unless there is a reason to doubt the objective truth of the statements contained therein which are relied on for enabling support. *See M.P.E.P.* § 2164.04. *Id.* In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 7/23/07

By: _____

Brenden S. Gingrich
Registration No. 60,295
Attorney of Record
Customer No. 30,313
(619) 235-8550

4022659
071607

EXHIBIT 1

The opinion in support of the decision being entered today was *not* written for publication and is *not* binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte AUDREY GODDARD, PAUL J. GODOWSKI,
AUSTIN L. GURNEY, VICTORIA SMITH, and WILLIAM I. WOOD

Appeal 2006-1469
Application 10/123,212
Technology Center 1600

Decided: April 30, 2007

Before TONI R. SCHEINER, ERIC GRIMES, and LORA M. GREEN, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 72-79 and 82-84. We have jurisdiction under 35 U.S.C. § 6(b). Claims 72 and 77 are representative of the claims on appeal, and read as follows:

72. An isolated polypeptide having at least 80% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide of SEQ ID NO:14;

(b) the amino acid sequence of the polypeptide of SEQ ID NO:14, lacking its associated signal peptide; or

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203577,

wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells.

77. An isolated polypeptide comprising:

(a) the amino acid sequence of the polypeptide of SEQ ID NO:14;

(b) the amino acid sequence of the polypeptide of SEQ ID NO:14, lacking its associated signal peptide; or

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203577.

Claims 72-79 and 82-84 stand rejected under 35 U.S.C. § 101 as not being supported by either a specific and substantial utility or a well-established utility. Claims 72-76, 83, and 84 stand rejected under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification, and claims 72-76, 83, and 84 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description. Finally, 72-74, 83, and 84 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Young,[1] and claims 72-75, 83, and 84 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Stanton.[2]

We Affirm-In-Part.

---

[1] Young, US Patent No. 6,525,174 B1, issued February 25, 2003.
[2] Stanton, US Pub. No. 2002/0110804 A1, published August 15, 2002.

UTILITY

ISSUE

The Examiner contends that the Specification fails to establish a specific and substantial utility or a well-established utility of the polypeptide of SEQ ID NO:14.

Appellants contend that Example 30 presents microarray data demonstrating that the polypeptide of SEQ ID NO:14 is a diagnostic marker for colon, lung, and prostate tumors.

The issue is thus whether the microarray data presented in Example 30 of the Specification is sufficient to establish a specific and substantial utility or a well-established utility for the polypeptide of SEQ ID NO:14?

FACTS

The Examiner rejected claims 72-79 and 82-84 under 35 U.S.C. § 101 as not being supported by either a specific and substantial asserted utility or a well-established utility (Answer 4).

The Examiner notes that the Specification discloses the polypeptide of SEQ ID NO:14 (PRO1866), the nucleic acid sequence encoding it (SEQ ID NO:13), as well as antibodies against the polypeptide. (*Id.*)

As to a well-established utility, the Examiner asserts that the prior art does not demonstrate that the polypeptide of SEQ ID NO:14, the nucleic acid encoding the polypeptide or an antibody that binds to the polypeptide, has "any well-established biological functions or any physiological significance." (*Id.* at 4-5.)

Next, as to a specific and substantial utility, the Examiner references Table 8 of the Specification, which states that the polypeptide is

significantly overexpressed in colon, lung, or prostate tumors compared to a non-cancerous human tissue control. (*Id.* at 5.) The Examiner also notes that the statement is based on a microarray analysis, which measures mRNA levels, and not overexpression of the polypeptide of SEQ ID NO:14 itself. (*Id.*) According to the Examiner:

> There is no sufficient information or experimental data presented on whether the polypeptide or the nucleic acid of the present invention can serve as a reliable diagnostic marker for colon, lung or prostate tumors; there is no statistical analysis of the expression data. Moreover, the assay does not establish a causative link between the polypeptide (or nucleic acid) of the present invention and colon, lung or prostate tumors. Without such critical information, one skilled in the art would not be able to use the molecule of the present invention as a diagnostic marker or as a therapeutic target for treatment of colon, lung or prostate tumors without undue experimentation. Accordingly, the results in Table 8 obtained based upon the assay described in Example 30 only serve as the beginning point for further research on the biological functions or physiological significance of the polypeptide of SEQ ID NO:[]14 or the nucleic acid encoding the polypeptide, and does not provide a specific and substantial utility for the present invention.

(*Id.* at 5-6.)

Appellants argue that patentable utility is demonstrated by Example 30 of the Specification (Br. 4). According to Appellants, Example 30 demonstrates that the gene encoding the polypeptide of PRO1866 (SEQ ID NO:14) "showed significant overexpression in colon, lung, and prostate tumors as compared to a universal normal control," demonstrating "'that the PRO polypeptides of the present invention are useful . . . as diagnostic markers for the presence of one or more cancerous tumors . . . .'" (*Id.*)

Appellants argue further that it is legally incorrect for the Examiner to require specific data, statistical analysis, and further details before accepting the utility set forth in the Specification, as the law is clear that the Examiner must accept Appellants' assertion of utility if that assertion would be credible to one of ordinary skill. (*Id.* at 4-5.)

Appellants assert that the Examiner has used an improper standard in asserting that mRNA levels do not necessarily correlate with the protein level and that protein levels cannot be accurately predicted from mRNA levels. (*Id.* at 6.) The evidentiary standard to be used during examination is preponderance of the evidence under the totality of the circumstances, and thus, Appellants argue, the Examiner "must establish that it is *more likely than not* that one of ordinary skill in the art would doubt the truth of the statement of utility," which "is a much lower standard than a 'necessary' correlation or 'accurate' prediction, and is clearly met for the invention claim." (*Id.* (emphasis in original)).

Moreover, Appellants rely on the Declaration of Dr. Paul Polakis, which states that "*in general, there is a correlation between mRNA levels and polypeptide levels.*" (Br. 6 (emphasis in original)). Appellants also rely on the Declaration of Dr. Victoria Smith, which states that "*microarray analyses actually performed in my laboratory* have shown that when molecules are identified as being overexpressed in a human tumor sample of epithelial origin relative to the 'universal normal control'[3] sample, *in a majority of cases*, that molecule is also confirmed as being overexpressed in

[3] The "universal" epithelial control sample is prepared by pooling non-cancerous human tissues of epithelial origin, including liver, kidney, and lung (Br. 12).

the human tumor tissue sample relative to its human tissue counterpart" (Br. 6 (emphasis in original)). Appellants aver that the two declarations support the assertion of utility in the Specification, *i.e.*, that the PRO1866 polypeptide (SEQ ID NO:14) "is reasonably expected to be overexpressed in colon, lung and prostate tumors and can be used as a cancer diagnostic marker." (*Id.* at 6-7.)

The Specification is drawn to the identification and isolation of novel DNA and to the recombinant production of polypeptides (Specification 1).

Example 30 on page 134 of the Specification is drawn to microarray analysis to detect PRO polypeptides in cancerous tumors.

According to the Specification:

> In the present example, cancerous tumors derived from various human tissues were studied for PRO polypeptide-encoding gene expression relative to non-cancerous human tissue in an attempt to identify those PRO polypeptides which are overexpressed in cancerous tumors. Two sets of experimental data were generated. In one set, cancerous human colon tumor tissue and matched non-cancerous human colon tumor tissue from the same patient ("matched colon control") were obtained and analyzed for PRO polypeptide expression using . . . microarray technology. In the second set of data, cancerous human tumor tissue from any of a variety of different human tumors was obtained and compared to a "universal" epithelial control sample which was prepared by pooling non-cancerous human tissues of epithelial origin, including liver, kidney, and lung. mRNA isolated from the pooled tissues represents a mixture of expressed gene products from these different tissues. Microarray hybridization experiments using the pooled control samples generated a linear plot in a 2-color analysis. The slope of the line generated in a 2-color analysis was then used to normalize the ratios of (test:control detection) within each experiment. The normalized ratios from various experiments were then compared and used to identify clustering

> of gene expression. Thus, the pooled "universal control" sample not only allowed effective relative gene expression determinations in a simple 2-sample comparison, it also allowed multi-sample comparisons across several experiments.
>
> In the present experiments, nucleic acid probes derived from the herein described PRO polypeptide-encoding nucleic acid sequences were used in the creation of the microarray and RNA from the tumor tissues listed above were used for the hybridization thereto. A value based upon the normalized ratio:experimental ratio was designated as a "cutoff ratio". Only values that were above this cutoff ratio were determined to be significant. Table 8 below shows the results of these experiments, demonstrating that various PRO polypeptides of the present invention are significantly overexpressed in various human tumor tissues as compared to a non-cancerous human tissue control. As described above, these data demonstrate that the PRO polypeptides of the present invention are useful not only as diagnostic markers for the presence of one or more cancerous tumors, but also serve as therapeutic targets for the treatment of those tumors.

(*Id.* at 134-35.)

As to PRO1866, the Specification presents Table 8, which states that PRO1866 is overexpressed in colon tumor, prostate tumor, and lung tumor, as compared to universal normal control. (*Id.* at 135.)

The Declaration of Dr. Paul Polakis, dated September 9, 2005, states in paragraphs 4 and 5 that, based on experience with other gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells, it has been observed "that there is a strong correlation between changes in the level of mRNA present in any particular cell type and the level of protein expressed from that mRNA in that cell type. In approximately 80% of our observations we have found that increases in the level of a particular mRNA correlates with changes in the

level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells."

The Declaration of Dr. Victoria Smith at paragraph 5, dated September 9, 2005, states that the comparison of mRNA expression levels in human tumor tissues to mRNA expression levels in a sample prepared by pooling non-cancerous human tissues of epithelial origin "is extremely informative and provides a strong basis for the diagnostic determination of cancer in humans."

PRINCIPLES OF LAW

The examiner bears the initial burden of showing that a claimed invention lacks patentable utility. *See In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). ("Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.").

The Court of Appeals for the Federal Circuit addressed the utility requirement in *In re Fisher*, 421 F.3d 1365, 76 USPQ2d 1225 (Fed. Cir. 2005). The *Fisher* court interpreted *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966), as rejecting a "de minimis view of utility." 421 F.3d at 1370, 76 USPQ2d at 1229. The *Fisher* court held that § 101 requires a utility that is both substantial and specific. *Id.* at 1371, 76 USPQ2d at 1229. The court held that disclosing a substantial utility means "show[ing] that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. Simply put, to

satisfy the 'substantial' utility requirement, an asserted use must show that that claimed invention has a significant and presently available benefit to the public." *Id.*, 76 USPQ2d at 1230.

The court held that a specific utility is "a use which is not so vague as to be meaningless." *Id.* In other words, "in addition to providing a 'substantial' utility, an asserted use must show that that the claimed invention can be used to provide a well-defined and particular benefit to the public." *Id.*

ANALYSIS

We find that the microarray data presented in Example 30 of the Specification is sufficient to establish a specific and substantial utility for the polypeptide of SEQ ID NO:14, and the rejection is reversed.

The microarray data demonstrates that mRNA for the PRO1866 polypeptide (SEQ ID NO:14) is overexpressed in colon tumor, prostate tumor, and lung tumor, as compared to universal normal control. Thus, the polypeptide of SEQ ID NO:14 has a significant and presently available benefit to the public as a tumor marker.

We have considered the Examiner's assertions that microarray analysis measures mRNA levels, and not overexpression of the polypeptide of SEQ ID NO:14 itself. As demonstrated by the Polakis and Smith Declarations, however, there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that.

Finally, the use of the PRO1866 polypeptide as a cancer marker is sufficient to demonstrate utility, and there is no requirement that a causative

link between the polypeptide (or nucleic acid) of the present invention and colon, lung or prostate tumors be demonstrated.

ENABLEMENT

ISSUE

The Examiner contends that the disclosure does not enable one skilled in the art to practice the full genus of peptides encompassed by Appellants' claims.

Appellants contend that one skilled in the art could practice the full scope of the claimed invention, as the skilled artisan has a sufficiently high level of technical competence to identify sequences with at least 80% identity to SEQ ID NO:14, and the specification provides ample guidance such that one of skill in the art could readily test the nucleic acid encoding a variant polypeptide to determine whether it is overexpressed in colon, lung or prostate tumors by the methods set forth in Example 30.

Thus, the issue is does the Specification enable one skilled in the art to use the full scope of the PRO1866 (SEQ ID NO:14) variants of claim 72 without an undue amount of experimentation?

FACTS

The Examiner rejected claims 72-76, 83, and 84 under 35 U.S.C. § 112, first paragraph, on the grounds that the instant disclosure does not enable the full scope of the claimed subject matter (Answer 7).[4]

As we find that Appellants do not argue the claims separately, we focus our attention on independent claim 72. 37 C.F.R. § 41.37(c)(1)(vii) (2006).

The Examiner made the following findings with respect to the factors set out in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).[5]

The breadth of the claims: The Examiner notes that the claims are broad and encompass a genus of variants of SEQ ID NO:14 (Answer 8).

Nature of the invention and the state of the prior art: The Examiner notes that while the Specification teaches that the polypeptide of SEQ ID NO:14 is overexpressed in colon, lung or prostate tumors, the polypeptide "does not have any defined biological functions or activities." (*Id.*)

---

[4] The Examiner also rejected claims 72-79 and 82-84 under 35 U.S.C. § 112, first paragraph, on the grounds that "since the claimed invention is not supported by either a specific and substantial utility or a well established utility . . ., one skilled in the art clearly would not know how to use the claimed invention" (Answer 7). Since that rejection relies on the utility rejection, and as we have reversed that rejection, this rejection is also reversed.

[5] The factual considerations discussed in *Wands* are: (1) the quantity of experimentation necessary to practice the invention, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Examiner notes further that two variants of the polypeptide of SEQ ID NO: 14 are taught in the prior art by Young (a variant having 92.5% homology) and Stanton (a variant having 96.7% identity), but does not teach that the variants are overexpressed in colon, lung, or prostate tumor cells (Answer 8-9). The Examiner also asserts, citing Haynes,[6] that even if the amount of nucleic acid expressed from SEQ ID NO:13 was overexpressed in colon, lung, or prostate tumor cells, it does not necessarily follow that the polypeptide of SEQ ID NO:14 would also be overexpressed.

The amount of direction or guidance presented and the existence of working examples: The Examiner states that, other than for the polypeptide of SEQ ID NO:14, the Specification fails to provide sufficient direction and/or working examples to make those variants that have the same functions as SEQ ID NO:14, and that there are no examples of functional variants of SEQ ID NO:14 (Answer 9). The Examiner notes further that the Specification does not teach which residues are critical to activity, and thus which modifications will results in a variant having the same function as that of SEQ ID NO:14. (*Id.* at 9-10.)

The relative skill of those in the art, the predictability or unpredictability of the art, and the quantity of experimentation necessary: While acknowledging that the level of skill in the art of DNA recombination technology is relatively high, the Examiner states that procedures for making

---

[6] Haynes et al. (Haynes), "Proteome analysis: Biological assay or data archive," *Electrophoresis*, Vol. 19, pp. 1862-1871 (1998). The Examiner cites Haynes for the proposition that "[t]he prior art teaches that the multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (Answer 9).

variants of the polypeptide of SEQ ID No: 14 as set forth by the claims that still retain its activity are not conventional and are unpredictable. (*Id.* at 10.) The Examiner concludes that "due to lack of the disclosure of the functions of encompassed polypeptides structurally related to SEQ ID NO:14, [lack of] sufficient guidance and/or working examples provided in the specification, and [lack of] teachings in the art on how to use those variants of the polypeptide of SEQ ID NO:14, it would take undue experimentation for one skilled in the art to make and use the variants of polypeptide of SEQ ID NO:14." (*Id.* at 10-11.)

Appellants argue that "the claimed variants all share the functional limitation that '*the nucleic acid encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells*," and that Example 30 of the Specification provides step-by-step guidelines and protocols for the microarray analysis (Br. 28 (emphasis in original)). Appellants assert further that "[t]he specification provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 81, line 17, to page 83, line 26)" (Br. 29).

Appellants submit

> that the specification provides ample guidance such that one of skill in the art could readily test the nucleic acid encoding a variant polypeptide to determine whether it is overexpressed in colon, lung or prostate tumors by the methods set forth in Example 30. Furthermore, one of ordinary skill in the art has a sufficiently high level of technical competence to identify sequences with at least 80% identity to SEQ ID NO:14. Accordingly, one of ordinary skill could practice the claimed invention without undue experimentation.
>
> The claims currently recite polypeptide sequences associated with a specific biological activity of the encoding nucleic acid. This biological activity together with the well

> defined relatively high degree of sequence identity and general knowledge in the art at the time the invention was made, sufficiently defines the claimed genus such that, one skilled in the art, at the effective date of the present application, would have known how to make and use the claimed polypeptide sequences without undue experimentation.

(*Id.*)

As noted with respect to the utility rejection, Table 8 of the Specification states that PRO1886 is overexpressed in colon tumor, prostate tumor, and lung tumor, as compared to universal normal control. (Specification 135.)

Page 81, line 17 to page 83, line 26 of the Specification provides general guidance as to the generation of PRO polypeptide variants, which guidance is applicable to the generation of any polypeptide variant. The Specification does not disclose any guidance that is specific to the PRO1866 (SEQ ID NO:14) polypeptide. The Specification also does not present any data as to the biological function of PRO1866 other than the microarray data that demonstrates that it may be used as a tumor marker.

PRINCIPLES OF LAW

Enablement is a question of law, based on underlying findings of fact. *See, e.g., In re Wands*, 858 F.2d 731, 735, 8 USPQ2d 1400, 1402 (Fed. Cir. 1988). "When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the

invention provided in the specification of the application." *In re Wright*, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

"[T]o be enabling, the specification . . . must teach those skilled in the art how to make and use *the full scope of the claimed invention* without 'undue experimentation.'" *Wright*, 999 F.2d at 1561, 27 USPQ2d at 1513 (emphasis added), *quoted in Genentech, Inc. v. Novo Nordisk, A/S,* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997). Thus, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed." *In re Vaeck*, 947 F.2d 488, 496 & n. 23, 20 USPQ2d 1438, 1445 & n. 23 (Fed. Cir. 1991), *quoted in Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1372, 52 USPQ2d 1129, 1138 (Fed. Cir. 1999).

"Patent protection is granted in return for an enabling disclosure . . . , not for vague intimations of general ideas that may or may not be workable." *Genentech*, 108 F.3d at 1365, 42 USPQ2d at 1005. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, *reasonable detail* must be provided in order to enable members of the public [skilled in the art] to understand and carry out the invention." *Id.* at 1366, 42 USPQ2d at 1005 (emphasis added).

ANALYSIS

While Appellants have demonstrated that the polypeptide of SEQ ID NO:14 is a diagnostic marker for colon, lung, and prostate cancer, the Specification sets forth no biological activity or function for the protein. All

that is disclosed is the sequence information for SEQ ID NO:14. Moreover, the Specification does not disclose which portions of the polypeptide of SEQ ID NO:14 are required for activity, and which regions are tolerant to substitution. With respect to the variants, all that is disclosed by the Specification are methods of making polypeptide variants in general, and information as to what amino acid substitutions are generally considered by the skilled artisan to be conservative. The Specification, however, does not disclose any guidance of generating variants of the polypeptide of SEQ ID NO:14 that is specific to SEQ ID NO:14, wherein the variant is overexpressed in colon, lung, or prostate tumor cells.

Without information as to the biological activity or function, it would be unpredictable to the skilled artisan which variants of SEQ ID NO:14 would also perform as a diagnostic marker for colon, lung, and prostate cancer. Claim 72 is drawn to variants having 80% amino acid sequence identity, but, as noted by the Examiner, two variants of the polypeptide of SEQ ID NO:14 having higher sequence identity have been disclosed by Young (a variant having 92.5% homology) and by Stanton (a variant having 96.7% identity), but have not been shown to be overexpressed in colon, lung, or prostate tumor cells.

Given the lack of guidance as to the biological function or activity of the polypeptide of SEQ ID NO:14, and the lack of guidance as to those variants of SEQ ID NO:14 that would be expected to also perform as a diagnostic marker for colon, lung, and prostate cancer, as well as the enormous number of variants that would have 80% sequence identity with

SEQ ID NO:14,[7] it would require an undue amount of experimentation by one skilled in the art to use the full scope of variants encompassed by claim 72 without further guidance from Appellants.

CONCLUSIONS OF LAW

We conclude that the Specification does not enable one skilled in the art to use the full scope of the PRO1866 (SEQ ID NO:14) variants of claim 72 without an undue amount of experimentation, and the rejection is affirmed.

WRITTEN DESCRIPTION

ISSUE

The Examiner contends that the claims are drawn to an isolated polypeptide having 80%, 85%, 90%, 95%, and 99% sequence identity to SEQ ID NO:14, and due to the breadth of the claimed genus and the lack of definitive structural or functional features of the claimed genus, one skilled in the art would not recognize from the disclosure that the Appellants were in possession of the claimed genus

Appellants contend that the genus of polypeptides with at least 80% sequence identity to SEQ ID NO:14, which possess the functional property of having a nucleic acid which is overexpressed in colon, lung or prostate tumors, would meet the requirement of 35 U.S.C. § 112, first paragraph, as providing adequate written description.

---

[7] The polypeptide of SEQ ID NO:14 is 541 amino acids long, and as there are 20 naturally occurring peptides, the number of variants that would have 80% sequence identity to SEQ ID NO:14 would be enormous.

Thus, the issue is does the disclosure as filed provide adequate written description to support the genus of variants of the polypeptide of SEQ ID NO:14 encompassed by claim 72?

FACTS

The Examiner rejected claims 72-76, 83, and 84 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention (Answer 11).

As we find that Appellants do not argue the claims separately, we focus our attention on independent claim 72. 37 C.F.R. § 41.37(c)(1)(vii) (2006).

The Examiner notes that the claims are drawn to an isolated polypeptide having 80%, 85%, 90%, 95%, and 99% sequence identity to SEQ ID NO:14, asserting that the claims do not require that the polypeptide have any particular conserved structure or any other distinguishing feature. (Answer 12.) According to the Examiner,

> [w]hile the claims recite a limitation "wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells," such a limitation does not limit the scope of the invention in actuality because the specification does not reasonably identify or confirm that the polypeptide or the nucleic acid encoding the polypeptide is overexpressed in colon, lung or prostate tumor cells. Thus, the claims are drawn to a genus of polypeptides that is defined only by a partial structure in the form of a recitation of percent identity.

(*Id.*)

Moreover, according to the Examiner, the disclosure of SEQ ID NO:14 and its encoding nucleic acid sequence, SEQ ID NO:13, "does not adequately support the scope of the claimed genus, which encompasses a substantial variety of homologues or variants of the polypeptide of SEQ ID NO:14." (*Id.*) The disclosure as filed, the Examiner asserts, fails to provide sufficient description as to structural and functional features of the claimed genus, such as conserved regions that are critical to the structure and function of the genus claimed. (*Id.* at 13.) Thus, "[t]here is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function." (*Id.*)

The Examiner concludes:

> Due to the breadth of the claimed genus and lack of the definitive structural or functional features of the claimed genus, one skilled in the art would not recognize from the disclosure that the Appellant was in possession of the claimed genus. Accordingly, only the isolated polypeptide comprising SEQ ID NO:14 . . ., but not the full breadth of the claims meets the written description provision of 35 U.S.C. § 112, first paragraph.

(*Id.* at 13-14.)

Appellants assert that "the genus of polypeptides with at least 80% sequence identity to SEQ ID NO:14, which possess the functional property of having a nucleic acid which is overexpressed in colon, lung or prostate tumors would meet the requirement of 35 U.S.C. § 112, first paragraph, as providing adequate written description." (Br. 32.) According to Appellants, the level of skill in the art of recombinant DNA technology is high, and thus "the teachings imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made." (*Id.*)

Appellants argue further that Example 30 provides step-by-step guidelines and protocols for performing the microarray analysis, thus the skilled artisan could test variants of the PRO1866 polypeptide (SEQ ID NO:14) to determine if they are overexpressed in colon, lung, or prostate tumor cells. (*Id.*) Moreover, Appellants aver, the Specification (page 81, line 17, to page 83, line 26) provides detailed guidance as to what changes may be made to the PRO polypeptide without affecting its activity, such as exemplary and preferred amino acid substitutions (Br. 33). "Accordingly," Appellants assert, "one of skill in the art could identify whether a variant PRO1866 sequence falls within the parameters of the claimed invention." (*Id.*).

Appellants note that factors to be considered in evidencing possession of a claimed genus include structural features and functional activity, which they assert they have provided by reciting a structural feature—80% sequence identity to SEQ ID NO:14—as well as a specific functional activity for the encoding nucleic acids. (*Id.*)

As noted above with respect to the enablement rejection, page 81, line 17 to page 83, line 26 of the Specification provides general guidance as to the generation of PRO polypeptide variants. The Specification does not disclose any guidance that is specific to the PRO1866 (SEQ ID NO:14) polypeptide. The Specification also does not present any data as to the biological function of PRO1866 other than the microarray data that demonstrates that it may be used as a tumor marker.

PRINCIPLES OF LAW

The requirement for written description under the first paragraph of section 112 is separate and distinct from the enablement requirement of that paragraph. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1116-17 (Fed. Cir. 1991). Compliance with the written description requirement is a question of fact. *Id.*

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997 (bracketed material in original). The claims in *Lilly* were directed generically to vertebrate or mammalian insulin cDNAs. *See id.* at 1567, 43 USPQ2d at 1405. The court held that a structural description of a rat cDNA was not an adequate description of these broader classes of cDNAs.

The *Lilly* court explained that

> a generic statement such as. . . 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus.

Id. at 1568, 43 USPQ2d at 1406. Finally, the *Lilly* court set out exemplary ways in which a genus of cDNAs could be described:

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by

> nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Id. at 1569.

Our appellate reviewing court revisited the issue of describing DNA. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The *Enzo* court held that a claimed DNA could be described without, necessarily, disclosing its structure. The court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'" *See id.* at 1324, 63 USPQ2d at 1613 (emphasis omitted, ellipsis and bracketed material in original).

Our appellate review court has also noted that "*Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332, 65 USPQ2d 1385, 1398 (Fed. Cir. 2003).

This standard applies to polypeptides as well as DNAs. *See University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 925, 69 USPQ2d 1886, `893 (Fed. Cir. 2004): "We agree with Rochester that *Fiers*,

Lilly, and *Enzo* differ from this case in that they all related to genetic material whereas this case does not, but we find that distinction to be unhelpful to Rochester's position. It is irrelevant; the statute applies to all types of inventions. We see no reason for the rule to be any different when non-genetic materials are at issue."

With respect to the use of an assay to support written description, in *University of Rochester*, the patent claimed a method of selectively inhibiting the enzyme PGHS-2 (also known as COX-2) by "administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product in a human." *Id.* at 918, 69 USPQ2d at 1888. The patent "described in detail how to make cells that express either COX-1 or COX-2, but not both . . . , as well as 'assays for screening compounds, including peptides, polynucleotides, and small organic molecules to identify those that inhibit the expression or activity of the PGHS-2 gene product.[']" *Id.* at 927, 69 USPQ2d at 1895.

The court held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of *which* peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. *See id.* ("As pointed out by the district court, the '850 patent does not disclose just 'which "peptides, polynucleotides, and small organic molecules" have the desired characteristic of selectively inhibiting PGHS-2.' . . . Without such disclosure, the claimed methods cannot be said to have been described.").

ANALYSIS

We find that the disclosure as filed does not provide adequate written description to support the genus of variants of the polypeptide of SEQ ID NO:14 encompassed by claim 72, and the rejection is affirmed.

Claim 72 is drawn to variants that have 80% sequence identity to SEQ ID NO:14, wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells. The Specification does not disclose a biological function or activity of the polypeptide of SEQ ID NO:14, and also does not disclose a single variant that also performs as a diagnostic marker for colon, lung, and prostate cancer. Thus, the genus encompasses an enormous number of sequences, but the Specification only describes a single member of that genus—SEQ ID NO:14.

In addition, there is no disclosure of sufficiently detailed, relevant identifying characteristics, such as other physical and/or chemical properties, or functional characteristics, that when coupled with a known or disclosed correlation between function and structure (i.e., the sequence), or some combination of such characteristics, would constitute an adequate written description of the claimed invention. All that is disclosed is the amino acid sequence and that it may be used as a diagnostic marker for certain tumor types. While the skilled artisan may be able to determine polypeptides that have 80% sequence identity with SEQ ID NO:14, without any disclosure of function or what residues are required for the polypeptide to function as a diagnostic marker, the skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus that would be useful as a diagnostic marker.

Moreover, just as in the *University of Rochester* case, discussed above, the present application discloses a broad genus of chemical compounds (polypeptides having 80% sequence identity to SEQ ID NO:14) but the claims are limited to only those compounds having a desired characteristic (wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung, or prostate tumor cells). Just as in *University of Rochester*, the present specification does not disclose which nucleic acids encoding the many possible polypeptides having 80% sequence identity to SEQ ID NO:14 are overexpressed in colon, lung, or prostate tumor cells.

Granted, those skilled in the art could screen libraries of naturally occurring DNAs for overexpression in colon, lung or prostate tumor cells to identify for themselves specific DNAs that encode polypeptides having 80% sequence identity to SEQ ID NO:14. That, however, does not make up for the deficiency of the specification's description. The *University of Rochester* court specifically noted that the patent at issue there disclosed screening assays to identify compounds having the desired characteristic, but nonetheless held that the description was inadequate. The same holds true here.

PRIOR ART

ISSUE

The Examiner contends that claims 72-74, 83, and 84 are anticipated by Young, and that claims 72-75, 83, and 84 are anticipated by Stanton.

Appellants contend that have demonstrated invention prior to the effective filing dates of Young and Stanton, and thus Young and Stanton are not anticipatory art within the meaning of 35 U.S.C. § 102(e).

Thus, the issue is whether the Declaration submitted under 37 C.F.R. § 1.131 is sufficient to overcome the rejections over the prior art made under 35 U.S.C. § 102(e)?

FACTS

The Examiner rejected claims 72-74, 83, and 84 under 35 U.S.C. § 102(e) as being anticipated by Young (Answer 14).

According to the Examiner, Young teaches a polypeptide that shares 92.5% sequence identity with SEQ ID NO:14. (*Id.*)

The Examiner rejected claims 72-75, 83, and 84 under 35 U.S.C. § 102(e) as being anticipated by Stanton. (*Id.* at 15.)

According to the Examiner, Stanton teaches a polypeptide that shares 96.7% sequence identity with SEQ ID NO: 14. (*Id.*)

Appellants do not argue the merits of the rejections. Rather, Appellants assert that the declaration submitted under 37 C.F.R. § 1.131 is sufficient to show invention prior to the effective filing dates of Young and Stanton (Br. 34).

Appellants cite the 37 C.F.R. § 1.131 Declaration of Dr. Goddard, Dr. Godawski, Dr. Gurney, Dr. Smith, and Dr. Wood, to support the proposition that the inventors "conceived and reduced to practice the PRO1866 polypeptide and its encoding nucleic acid sequence in the United States prior to December 4, 1998." (*Id.* (emphasis removed).) According to Appellants, "the Declaration clearly establishes that the claimed polypeptides and the nucleic acids encoding them, were conceived and reduced to practice prior to December 4, 1998, and that the differential expression of PRO1866 in the

multiple types of cancer cells based on microarray analysis were demonstrated prior to March 31, 2000." (*Id.* at 35.)

Appellants cite MPEP § 715.03 for the proposition that:

> proof of prior completion of a species different from the reference species will be sufficient to overcome a reference indirectly under 37 C.F.R. § 1.131 if the reference species would have been obvious in view of the species shown to have been made by applicants. Alternatively, *the applicant may be able to antedate the reference indirectly by demonstrating possession of the claimed genus prior to the reference date.* The test is whether the species completed by applicant prior to the reference date provided an adequate basis for inferring that the invention has generic applicability. . . . The test is whether the facts set out in the affidavit are such as would persuade one skilled in the art that the applicant possessed so much of the invention as is shown in the reference. *In re Schaub*, 537 F.2d 509, 190 U.S.P.Q. 324 (C.C.P.A. 1976).

(Br. at 35-36 (footnote omitted) (emphasis in original)).

Appellants cite their arguments regarding the written description rejection, asserting that the "disclosed polypeptide of SEQ ID NO[:]14 is *representative for a genus encompassing its variants*." (*Id.* at 36.)

Appellants also cite Example 14 of the Synopsis of Application of Written Description Guidelines issued by the USPTO, which Appellants note states

> that protein variants meet the requirements of 35 U.S.C. § 112, first paragraph, as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins are routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the

> specified functional activity and at least 95% sequence identity to the reference sequence.

(Br. 36.)

The Declaration submitted under 37 C.F.R. § 1.131 of Dr. Audrey Goddard, Dr. Paul J. Godowski, DR. Austin Gurney, Dr. Victoria Smith, and Dr. William I. Wood, dated October 26, 2004, states at ¶10 that "[b]oth the DNA-44174 and the PRO1866 polypeptide sequences were obtained prior to December 4, 1998." It further states at ¶17 that "the microarray analysis of mRNA expression of PRO1866 in cancer cells was conducted prior to March 31, 2000, and the data indicate that the mRNA of PRO1866 is overexpressed in colon, lung, and prostate tumors."

PRINCIPLES OF LAW

A declaration under 37 C.F.R. § 1.131 must establish possession of either the whole invention claimed or of something falling within the claim such as a species of a claimed genus, such that the claim as a whole reads on it. *See In re Tanczyn*, 347 F.2d 830, 831-32, 146 USPQ 298, 300 (CCPA 1965); *see also* MPEP § 715.02

Where the disclosure in the prior art is only a single species of a genus claim, appellant can overcome the rejection through the use of a 131 declaration by showing prior possession of the species disclosed in the reference. *In re Stempel*, 241 F.2d 755, 759, 113 USPQ 77, 81 (CCPA 1957). If the species disclosed in the reference is different from the species that was disclosed in the 131 declaration, the 131 declaration can only overcome the reference if the species shown in the reference would have been obvious in view of the species shown to have been made by appellant.

See In re Clarke, 356 F.2d 987, 961, 148 USPQ 665, 668-69 (CCPA 1966). If appellant cannot show possession of the species of the reference, appellant may be able to antedate the reference by showing prior completion of one or more species such that appellant was in possession of the claimed genus. *See id.* Note it is not necessary that the evidence demonstrate that appellant viewed the invention as encompassing more than the species actually made, only that the evidence would persuade one skilled in the art that appellant possessed so much of the invention as is shown in the reference. *In re Schaub*, 537 F.2d 509, 512 131, 190 USPQ 324, 326 (CCPA 1976). *See also* MPEP 715.03.

ANALYSIS

The species disclosed by the Declaration submitted under 131 is different than that disclosed by either the Young or Stanton reference. In addition, we have already determined in reviewing the rejection under 35 U.S.C. § 112, first paragraph, for written description, that the disclosure of a single species, *i.e.*, the polypeptide of SEQ ID NO:14 does not demonstrate that Appellants had possession of the claimed genus. Thus, we need to determine if the species disclosed by Young and Stanton would be obvious over the polypeptide of SEQ ID NO:14.

Appellants' claim 72 is drawn to a polypeptide having 80% sequence identity to SEQ ID NO:14. Thus, the species of Young and Stanton are clearly encompassed by the claims. Moreover, Appellants disclose that the polypeptide is overexpressed in colon, lung or prostate tumor cells. As we have already found above, however, neither the Declaration nor the disclosure as filed provides guidance as to what regions are necessary for

activity, or what the biological activity is, other than its use as a diagnostic marker. Thus, we conclude that there is nothing in the Declaration or the disclosure as filed that would suggest to one of ordinary skill in the art the species disclosed by Young and Stanton, and thus that the polypeptide of SEQ ID NO:14 does not render obvious the species disclosed by Young and Stanton. *See In re Baird,* 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious.").

Thus, as the Declaration submitted under 37 C.F.R. § 1.131 is not sufficient to overcome the rejections over the prior art made under 35 U.S.C. § 102(e), the rejections of claims 72-74, 83, and 84 under 35 U.S.C. § 102(e) as being anticipated by Young, and claims 72-75, 83, and 84 under 35 U.S.C. § 102(e) as being anticipated by Stanton, are affirmed.

CONCLUSION

In summary, we reverse the rejection of claims 72-79 and 82-84 under 35 U.S.C. § 101 as not being supported by either a specific and substantial utility or a well-established utility. We do, however, affirm the rejection of claims 72-76, 83, and 84 under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification; the rejection claims 72-76, 83 and 84 under 35 U.S.C. § 112, first paragraph, as lacking adequate written description; the rejection of claims 72-74, 83 and 84 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Young; and the rejection of claims 72-75, 83 and 84 under 35 U.S.C. § 102(e) as being anticipated by Stanton.

AFFIRMED-IN-PART

lbg

Ginger R. Dreger
Knobbe Martens Olson & Bear
201 California Street, Suite 1150
San Francisco CA 94111

EXHIBIT 2

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/123,212	04/15/2002	Audrey Goddard	P3330R1C35	5610

7590 11/03/2005

EXAMINER
LI, RUIXIANG

ART UNIT	PAPER NUMBER
1646	

Ginger R. Dreger
Knobbe Martens Olson & Bear
201 California Street, Suite 1150
San Francisco, CA 94111

DATE MAILED: 11/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/123,212
Filing Date: April 15, 2002
Appellant(s): GODDARD ET AL.

Panpan Gao
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 9, 2005 appealing from the Office action mailed December 17, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is essentially correct, except that there is no sufficient support for appellant's assertion that the PRO1866 mRNA or polypeptide is overexpressed in tumors as compared to a normal control.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal in the brief is correct.

(7) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Prior Art of Record

- Hu et al., Analysis of genomic and proteomic data using advanced literature mining. Journal of Proteome Research 2:405-412, 2003.
- Haynes et al., Proteome analysis: biological assay or data archive? Electrophoresis 19: 1862-1871, 1998.
- Wary et al., Analysis of VEGF-responsive genes involved in the activation of endothelial cells. Molecular Cancer 2:25, 2003.
- Yang et al., Vascular endothelial growth factor-induced genes in human umbilical vein endothelial cells. Arterioscler Thromb Vasc Biol 22:1797-1803, 2002.
- Young et al., U. S. Patent No. 6,525,174 B1, Feb. 25, 2003; filing date: Dec. 4, 1998.
- Stanton et al., U. S. 2002/0110804 A1, Aug. 15, 2002; 102(e) date : March 31, 2000).

The last two references cited by the Examiner are overlooked by the Appellant.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections—35 U.S.C. § 101

(i). 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

(ii). Claims 72-79 and 82-84 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Claims 72-79 and 82 are drawn to an isolated polypeptide comprising SEQ ID NO: 14 and its variants, whereas claims 83 and 84 are drawn to a chimeric polypeptide comprising the polypeptide. The claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. A specific and substantial utility is one that is particular to the subject matter claimed and that identifies a "real world" context of use for the claimed invention which does not require further research.

The specification discloses the polypeptide of SEQ ID NO: 14 (or PRO1866), the nucleic acid of SEQ ID NO: 13 encoding the polypeptide, and antibodies against the polypeptide. Nonetheless, the instant disclosure fails to provide any sufficient information or evidence on the specific biological functions or physiological significance of the molecules of the present invention and fails to disclose a patentable utility for the claimed invention.

First, the invention lacks a well-established utility. A well-established utility is a specific, substantial, and creditable utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material. The sequence and prior art search does not reveal that the polypeptide of SEQ ID NO: 14, the nucleic acid

encoding the polypeptide or an antibody that binds to the polypeptide has any well-established biological functions or any physiological significance. No art of record discloses or suggests any property or activity for the claimed molecules such that another non-asserted utility would be well-established for the claimed invention.

Secondly, the present invention does not disclose a specific and substantial utility. Table 8 of page 135 lists that the polypeptide of SEQ ID NO: 14 is significantly overexpressed in colon, lung or prostate tumors as compared to a non-cancerous human tissue control. The specification asserts that the polypeptide of the present invention is useful not only as a diagnostic marker for the presence of one or more cancerous tumors, but also serve as a therapeutic target for the tumor treatment (page 135). The Examiner notes that such an assay using microarray analysis as described in Example 30 merely measures the mRNA level; it does not measure the over-expression of the polypeptide of SEQ ID NO: 14. There is no sufficient information or experimental data presented on whether the polypeptide or the nucleic acid of the present invention can serve as a reliable diagnostic marker for colon, lung or prostate tumors; there is no statistical analysis of the expression data. Moreover, the assay does not establish a causative link between the polypeptide (or nucleic acid) of the present invention and colon, lung or prostate tumors. Without such critical information, one skilled in the art would not be able to use the molecule of the present invention as a diagnostic marker or as a therapeutic target for treatment of colon, lung or prostate tumors without undue experimentation. Accordingly, the results in Table 8 obtained based upon the assay

described in Example 30 only serve as the beginning point for further research on the biological functions or physiological significance of the polypeptide of SEQ ID NO: 14 or the nucleic acid encoding the polypeptide, and does not provide a specific and substantial utility for the present invention.

The specification also asserts that the nucleic acid sequences of the present invention may be used in gene therapy (the middle of page 94), the polypeptide may be employed as therapeutic agents (the middle of page 95), whereas the antibodies against the polypeptide of the present invention may be used in diagnostic assays (page 107). These asserted utilities are not specific and substantial because they do not identify or reasonably confirm a "real world" context of use. The specification fails to disclose the biological functions of the claimed molecules and any specific diseases that are associated with or can be treated with the claimed molecules. Clearly, further research would be required to identify a disease that is associated with the claimed molecules or a disease that can be treated with the claimed molecules. See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

The specification further asserts numerous uses of the molecules of the present inventions. For examples, the specification asserts that the nucleotide sequences have uses as hybridization probes, in chromosome and gene mapping and in the generation of anti-sense RNA and DNA, and are useful for the preparation of a polypeptide (page

91). However, such uses are all considered research uses only designed to identify a particular function of the claimed molecules and are not a substantial utility. See, e.g., *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966) wherein a research utility was not considered a "substantial utility."

In summary, all the asserted uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

Claim Rejections—35 U.S.C. § 112, First Paragraph, Enablement

(iii). Claims 72-79 and 82-84 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Furthermore, even if the polypeptide of SEQ ID NO: 14 were to have a patentable utility, the instant disclosure would not be found to be enabling for the full scope of the invention of claims 72-76, 83, and 84.

The factors that are considered when determining whether a disclosure satisfies

enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

The breadth of the claims. Claims 72-76 are drawn to an isolated polypeptide having at least 80%, 85%, 90%, 95%, and 99% sequence identity to the polypeptide of SEQ ID NO: 14, whereas claims 83 and 84 are drawn to a chimeric polypeptide comprising the polypeptide. Thus, the claims are broad and encompass a genus of variants of SEQ ID NO: 14. While the claims recite a limitation "wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells", such a limitation does not limit the scope of the invention in actuality because the specification does not reasonably identify or confirm that the polypeptide or the nucleic acid encoding the polypeptide is overexpressed in colon, lung or prostate tumor cells.

Nature of the invention and the state of the prior art. The present invention is related to the polypeptide of SEQ ID NO: 14, which does not have any defined biological functions or activities. The specification merely lists (Table 8 of page 135) that the polypeptide of SEQ ID NO: 14 is overexpressed in colon, lung or prostate tumors in the assay described in Example 30 without sufficient information, as noted above in the

utility rejection section. The prior art teaches two variants of the polypeptide of SEQ ID NO: 14 (U.S. Patent No. 6,525,174 B1; U.S. 2002/0110804 A1). However, the prior art does not teach that the variant of the polypeptide of SEQ ID NO: 14 is overexpressed in colon, lung or prostate tumor cells. Even if the nucleic acid of SEQ ID NO: 13 that encodes the polypeptide of SEQ ID NO: 14 were overexpressed in colon, lung or prostate tumor cells, the polypeptide of SEQ ID NO: 14 would not necessarily be overexpressed in colon, lung or prostate tumor cells because there is no correlative link established between the nucleic acid expression and the level of the polypeptide. The prior art teaches that the multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts (see, e.g., Haynes et al., Electrophoresis 19: 1862-1871, 1998, bottom of left column of page 1870).

The amount of direction or guidance presented and the existence of working examples. Other than the polypeptide set forth in SEQ ID NO: 14, the specification fails to provide sufficient direction and/or working example on how to make those variants and homologues that have the same function as that of the polypeptide of SEQ ID NO: 14 and on how to use those variants and homologues that do not have the same activity as that of the polypeptide of SEQ ID NO: 14. There are no examples of functional variants and homologues of SEQ ID NO: 14. While Figure 14 discloses the full-length polypeptide of SEQ ID NO: 14, the specification is silent with respect to which residues

may be altered without loss of activity. The instant disclosure does not show (i) which portions of the polypeptide of SEQ ID NO: 14 are critical to its activity; and (ii) what modifications (e.g., substitutions, deletions or additions) one can make to SEQ ID NO: 14 will result in a mutant or a fragment with the same functions as that of the polypeptide set forth in SEQ ID NO: 14.

The relative skill of those in the art, the predictability or unpredictability of the art, and the quantity of experimentation necessary. While the level of skill in the DNA recombination technology is relatively high, the microarray analysis has been widely used to determine the gene expression levels (Yang et al., Arterioscler Thromb Vasc Biol 22:1797-1803, 2002u et al., Journal of Proteome Research 2:405-412, 2003), the art does not teach that if a single polypeptide or a nucleic acid is overexpressed in a certain type of tumor as compared with a normal control, such as colon, lung or prostate tumors, variants of the polypeptide or nucleic acid will necessarily be overexpressed in the tumor. Procedures for making variants of SEQ ID NO: 14 which have at least 80% identity to SEQ ID NO: 14 and retains its recited activity are not conventional in the prior art. It is unpredictable whether a variant of SEQ ID NO: 14 would retain the same function as that of the full length of polypeptide of SEQ ID NO: 14. Thus, due to lack of the disclosure of the functions of encompassed polypeptides structurally related to SEQ ID NO: 14, sufficient guidance and/or working examples provided in the specification, and teachings in the art on how to use those variants of the polypeptide of SEQ ID NO: 14, it would take undue experimentation for one skilled in the art to make and use the

variants of the polypeptide of SEQ ID NO: 14.

Accordingly, even if the polypeptide of SEQ ID NO: 14 were to have a patentable utility, the instant disclosure would not be found to be enabling for the genus of polypeptides encompassed by the instant claims. Thus, it would require undue experimentation for one skilled in the art to make and use the claimed invention commensurate in scope with the claims.

Claim Rejections—35 U.S.C. § 112, First Paragraph, Written Description

(iii). The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(iv). Claims 72-76, 83, and 84 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics,

structure/function correlation, methods of making the claimed product, or any combination thereof.

Claims 72-76 are drawn to an isolated polypeptide having at least 80%, 85%, 90%, 95%, and 99% sequence identity to the polypeptide of SEQ ID NO: 14, whereas claims 83 and 84 are drawn to a chimeric polypeptide comprising the polypeptide. The claims do not require that the polypeptide possess any particular conserved structure nor other disclosed distinguishing feature. While the claims recite a limitation "wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells", such a limitation does not limit the scope of the invention in actuality because the specification does not reasonably identify or confirm that the polypeptide or the nucleic acid encoding the polypeptide is overexpressed in colon, lung or prostate tumor cells. Thus, the claims are drawn to a genus of polypeptides that is defined only by a partial structure in the form of a recitation of percent identity.

The instant disclosure of an isolated polypeptide of SEQ ID NO: 14 and its encoding nucleic acid molecule set forth in SEQ ID NO: 13 does not adequately support the scope of the claimed genus, which encompasses a substantial variety of homologues or variants of the polypeptide of SEQ ID NO: 14. A description of a genus of cDNA may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the

genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). While disclosing the amino acid sequence of SEQ ID NO: 14 (Figure 14), the instant disclosure fails to provide sufficient description information, such as definitive structural or functional features of the claimed genus of polypeptides. There is no description of the conserved regions that are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Moreover, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In the instant case, only one polypeptide sequence has been identified with *a potential link* to colon, lung or prostate tumors. No other species have been disclosed. One species is not adequately representative of the many sequences encompassed by the claims.

Furthermore, the prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to identify the encompassed polypeptides as being identical to those instantly claimed.

Due to the breadth of the claimed genus and lack of the definitive structural or functional features of the claimed genus, one skilled in the art would not recognize from the disclosure that the Appellant was in possession of the claimed genus. Accordingly, only

the isolated polypeptide comprising SEQ ID NO: 14 (and its mature form, i.e., lacking the signal peptide sequence), but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections—35 U.S.C. § 102 (e)

(v). The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(vi). Claims 72-74, 83, and 84 are rejected under 35 U.S.C. 102(e) as being anticipated by Young et al. (U.S. Patent No. 6,525,174 B1, Feb. 25, 2003; filing date: Dec. 4, 1998).

Young et al. teach a polypeptide that shares 92.5% sequence identity with SEQ ID NO: 14. Young et al. further teach a fusion protein comprising the polypeptide and an epitope tag, such as His-tag, HA-tag (Example 9; column 286). The art is silent regarding the cited functional limitation in the instant claims. However, all that appears to be necessary to achieve the cited functional limitation is the recited structural limitation which the art shares. Thus, the reference of Young et al. meets the limitations of claims 72-74, 83, and 84.

(vii). Claims 72-75, 83, and 84 are rejected under 35 U.S.C. 102(e) as being anticipated by Stanton et al. (U.S. 2002/0110804 A1, Aug. 15, 2002; 102 (e) date: March 31, 2000). Stanton et al. teach a polypeptide that shares 96.7% sequence identity with SEQ ID NO: 14. Stanton et al. further teach a fusion protein comprising the polypeptide and an immunoglobulin constant region (an Fc region; see [0197]). The art is silent regarding the cited functional limitation in the instant claims. However, all that appears to be necessary to achieve the cited functional limitation is the recited structural limitation which the art shares. Thus, the reference of Stanton et al. meets the limitations of claims 72-75, 83, and 84.

(10) Response to Argument

I. Rejection of claims 72-79 and 82-84 under the utility requirement of 35 USC §101

From the bottom of page 9 to the middle of page 12 of the Brief, Appellant, citing case law and MPEP, reviews the legal standard for utility, with which the Examiner takes no issue.

Beginning at page 12 of the Brief, Appellant argues that the microarray data disclosed in Example 30 establishes a credible, substantial and specific patentable utility for the PRO1866 polypeptide. Appellant argues that Example 30 and Table 8 explicitly states that PRO1866 is significantly overexpressed in colon, lung or prostate tumors as compared to the universal normal control. Appellant argues that the PRO1866 polypeptides are useful not only as diagnostic markers for the presence of one or more

cancerous tumors, but also serve as therapeutic targets for the treatment of those tumors.

Appellant's argument has been fully considered, but is not deemed to be persuasive for the following reasons. An assay using microarray analysis as described in Example 30 is essentially a hybridization assay. The only difference between microarray analysis and a simple hybridization is that a nucleic acid microarray often contains thousands of gene sequences. Thus, the microarray analysis merely measures the mRNA level; it does not measure the over-expression of the polypeptide of SEQ ID NO: 14. There is no evidence regarding whether the level of PRO1866 polypeptide of SEQ ID NO: 14 or, even more broadly, its variants significantly increased in colon, lung or prostate tumor samples in comparison with the normal control. There is no sufficient information or experimental data presented on whether the polypeptide or the nucleic acid of the present invention can serve as a reliable diagnostic marker for colon, lung or prostate tumors; there is no statistical analysis of the expression data. Moreover, the assay does not establish a causative link between the polypeptide (or nucleic acid) of the present invention and colon, lung or prostate tumors. Without such critical information, one skilled in the art would not be able to use the polypeptide of the present invention as a therapeutic target for treatment of colon, lung or prostate tumors without undue experimentation. The information disclosed in the instant specification is preliminary at best. Clearly further research would be required to determine whether the PRO1866 polypeptide can serve as a reliable diagnostic marker for colon, lung or prostate tumors

or as a therapeutic target for treatment of colon, lung or prostate tumors. Accordingly the claimed utility is not substantial.

The instant situation is analogous to what was addressed in Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct, 1966), where the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an application to engross what may prove to be a broad field", and "a patent is not a hunting license", "[it] is not a reward for the search, but compensation for its successful conclusion."

Beginning at the middle of page 13 of the Brief, Appellant, citing a statement from Dr. Smith's declaration, argues that the mRNA encoding PRO1866 shows significant overexpression in colon, lung or prostate tumors as compared to the universal normal control. Appellant argues that based upon the declaration by Dr. Smith and the teachings in the specification, one of ordinary skill would find it credible that the PRO1866 polypeptides of the present invention are useful as diagnostic markers for the presence of those colon, lung or prostate tumors.

Appellant's argument has been fully considered, but is not deemed to be persuasive for the reasons set forth immediately above. In addition, the declaration by Dr Smith states that molecules identified as being detectably overexpressed in a human tumor of epithelial origin as compared to the universal normal control are useful as diagnostic markers for the determination of the presence of that particular type of human tumor. However, Appellant concludes that the PRO1866 polypeptides are useful as diagnostic markers for colon, lung or prostate tumors. In doing so, the Examiner believes that Appellant's reasoning is flawed logically and does not account for a gap between a gene expression level and a protein level. The molecule detected by the microarray was one specific mRNA that is complementary to the nucleic acid of SEQ ID NO: 13 and encodes the polypeptide of SEQ ID NO: 14, not the polypeptide of SEQ ID NO: 14, not the variants of the polypeptide of SEQ ID NO: 14. There is no correlative link established between the level of gene expression and the level of the protein in general (see below for details).

Beginning at the 2nd paragraphs of page 14 of the Brief, Appellant criticizes a statement from the final rejection and argues that the diagnostic utility asserted in the present application is to be able to ***quantitatively*** compare the level of PRO1866 expression in a tumor sample to a normal control sample and to detect a ***relative*** difference in the level of PRO1866 expression between the tumor and normal samples.

Appellant's argument has been fully considered, but is not deemed to be persuasive because while listing merely PRO1866 molecule as being overexpressed in colon, lung or prostate tumors (Table 8 at page 135), the specification fails to provide either the actual level or the relative degree of the expression of PRO1866 polypeptide of SEQ ID NO: 14 or its encoding nucleic acid. There is no statistical analysis or validation analysis of the expression data. Numerous questions remain to be answered: such as how many tumor samples and normal control samples were used in the study? How were the normal control samples pooled? What types of colon, lung or prostate tumor samples were utilized in the assay (there are different types of lung tumors, for example)? What were the actual level or relative degree of expression of the protein or the nucleic acid encoding the polypeptide in the universal control versus the tumor samples? How to distinguish a truly positive hybridization signal from a false one? How many fold difference in the expression level between a tumor sample and a normal control was considered as being significant? Without such critical information, how would one of skill in the art be able to quantitatively compare the level of PRO1866 expression in a tumor sample to a normal control sample and to detect a relative difference in the level of PRO1866 expression between the tumor and normal samples?

Beginning at the 2nd paragraph of page 15 of the Brief, Appellant submits that the Examiner has overlooked the ample information provided in Example 30 for determining whether a gene is significantly overexpressed. In particular, the specification at page 134 offers ample information on how to ascertain the "cutoff ratio" for hybridization.

Appellant further submits the specification provides very clear guidelines as to how high levels must be to be deemed "significant".

Appellant's argument has been fully considered, but is not deemed to be persuasive because the specification discloses that if the hybridization signal of a probe from a test (disease tissue) sample is greater than hybridization signal of probe from control (normal tissue) sample, the gene or genes overexpressed in the disease are identified (lines 22-24 of page 134). The specification fails to disclose the specific "cutoff ratio". Is the "cutoff ratio" 1-fold, 5-fold, 10-fold, or 100-fold difference? The art cautions researchers from drawing conclusions based upon small changes in transcription levels between normal and cancerous tissue. For example, Hu et al. analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (Journal of Proteome Research 2:405-412, 2003). Hu et al. teach that there was no evidence of a correlation between altered gene expression and a known role in the disease for genes displaying a 5-fold change or less in tumors compared to normal. On the other side, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see, e.g., Abstract). If the "cutoff ratio" were disclosed in the specification to be 100-fold, for example, the nucleic acid of SEQ ID NO: 13 that encodes the PRO1866 polypeptide would likely to have a specific and substantial utility as a diagnostic marker for colon, lung or prostate tumors. However, it is not the case here. Most importantly, an assay

using microarray analysis as described in Example 30 merely measures the mRNA level; it does not measure the over-expression of the polypeptide of SEQ ID NO: 14 or its variants.

Beginning at the bottom of page 15 of the Brief, Appellant submits that Example 30 explicitly states that the PRO1866 mRNA and polypeptide are significantly overexpressed in colon, lung or prostate tumors as compared to the universal normal control. Appellant submits that Appellant should not be required to disclose the experimental details as long as Appellants provide the data showing that PRO1866 is significantly overexpressed in colon, lung or prostate tumors. Appellant further submits that the Examiner has not provided any evidence that one ordinary skilled in the art would doubt the credibility of the data in Example 30.

Appellant's argument has been fully considered, but is not deemed to be persuasive for the reasons set forth above.

At the 2nd paragraph of page 17 of the Brief, Appellant submits that the instant disclosure indicated that the experimental results disclosed in Table 8 of Example 30 are based upon reliable experimental design and solid statistical analysis.

Appellant's argument has been fully considered, but is not deemed to be persuasive because regardless how the experiments were designed, the specification simply fails

to disclose sufficient information to establish a specific and substantial utility for the claimed subject matter, as noted above.

At the 3rd paragraph of page 17 of the Brief, Appellant argues that Appellant merely claims that the observed and herein described differential expression profile of PRO1866 is diagnostic for the presence of only those colon, lung or prostate tumors that exhibit significant overexpression of PRO1866 as compared to the corresponding and respective normal tissue type or the universal control. Appellant submits that Appellant is not asserting a general diagnostic utility for the entire class of all human lung tumors, all human colon tumors, or all human prostate tumors, there is no need to demonstrate statistical significance across a wide range of different tumor types.

Appellant's argument has been fully considered, but is not deemed to be persuasive. First, Appellant's argument is a "circular" argument—PRO1866 is diagnostic for those colon, lung or prostate tumors that exhibit significant overexpression of PRO1866. It does not identify the specific type of tumor that can be diagnosed. Secondly, statistical analysis and validation analysis are needed to establish a marker for diagnosis of a certain type of tumor, for example, lung adenocarcinomas. A sufficient sample size (i.e., number of tumor samples and healthy control samples) is required for assessment of the difference in the expression level of a gene or protein at a given significance level (e.g., $P<0.01$). Without such an analysis, one of skill in the art would not be able to

judge whether a nucleic acid or a protein can be practically used as a diagnostic marker for a specific type of tumor.

Beginning at the bottom of page 17 of the Brief, Appellant argues that a prima facie case of lack of utility has not been established. Appellant submits that it is not a legal requirement to establish that increased mRNA expression "necessarily results in increased expression at the polypeptide level, or that protein levels can be accurately predicted. Appellant submits that the law requires only that one skilled in the art should accept that such a correlation is more likely than not to exist. Appellant argues that Haynes teaches that there was a general trend but no strong correlation between protein and transcript levels and there is a positive correlation between mRNA and protein amongst most of the 80 yeast proteins studied.

Appellant' argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, 35 U.S.C.§ 101 requires disclosure of a specific and substantial utility that is particular to the subject matter claimed and that identifies a "real world" context of use for the claimed invention without further research. In the instant case, there is no sufficient evidence on the record, either from the instant disclosure, Appellant's declaration or the prior art, which would reasonably identify or confirm the use of the polypeptide of SEQ ID NO: 14 and its variants as a diagnostic marker for colon, lung or prostate tumors. There is no sufficient evidence supporting Appellant's

assertion that it is more likely than not that the polypeptide of SEQ ID NO: 14 and its variants are overexpressed in colon, lung or prostate tumors.

Secondly, Appellant ignores the overall teachings of Haynes et al. At 2nd paragraph of left column of page 1863, Haynes et al. clearly states, "For some genes studied equivalent mRNA transcript level translated into protein abundances which varied by more than 50-fold. Similarly, equivalent steady state protein expression levels were maintained by transcript levels varying by as much as 40-fold". Clearly, Appellant's argument that a positive correlation exists between mRNA and protein is not true. Moreover, Haynes et al. conclude "The multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (bottom of left column of page 1870). Accordingly, the limited disclosure in the instant case does not meet the legal standard for a specific and substantial utility required under 35 U.S.C.§ 101.

Beginning at the 2nd paragraph of page 19 of the Brief, Appellant criticizes the publication of Hu et al. and claims that Hu et al. use different statistical methods to manipulate various aspects of the input data to affect the outcome, citing a statement from the article (4th paragraph of right column of page 406) as evidence.

Appellant' argument has been fully considered, but is not deemed to be persuasive because Hu et al. analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (Journal of Proteome Research 2:405-412, 2003). Hu et al. teach that there was no evidence of a correlation between altered gene expression and a known role in the disease for genes displaying a 5-fold change or less in tumors compared to normal. On the other side, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see, e.g., Abstract). Hu et al. listed systematic sources of false positives and false negatives in Table 1. Removing the false positives and false negatives would make the study more meaningful. For example, the false positive caused by gene symbol/name that is not unique is eliminated (see Table 1). This can only validate the data analysis, which is acceptable in the art as judged by the fact that the publication is a peer-reviewed article and cannot be said to be "manipulation of data to affect the outcome".

At the top of page 20 of the Brief, Appellant argues that the statistical analysis is not a reliable standard because the frequency of citation only reflects the current research interest in a molecule, not the true biological function of the molecule. Appellant also submits that it often happens in a scientific study that important molecules are overlooked by the scientific society for many years until the discovery of their true function.

Appellant' argument has been fully considered, but is not deemed to be persuasive because Hu et al. comprehensively summarize and estimates the relative strengths of all human gene-disease relationship in Medline, and analyzed a microarray expression dataset comparing breast cancer and normal breast tissue in the context of existing knowledge (see, e.g., Abstract). While it is true that "relationship established by frequency of co-citation do not necessarily represent a true biological link", as Hu et al. stated, "it is strong evidence to support a true relationship" (1st paragraph of right column of page 411). Further, while some functional molecules are not included in the analysis, a sample size of 2286 genes is sufficient to validate author's conclusion. The purpose of a statistical analysis is to predict the property or behavior of the overall population based upon analysis of a sample of the population.

At the 3rd paragraph of page 26 of the Brief, Appellant argues that the conclusion in Hu et al. only applies to a specific type of breast tumor (estrogen receptor-positive breast tumor) and cannot be generalized as a principle governing microarray study of breast cancer in general, let alone the various other types of cancer genes in general.

Appellant' argument has been fully considered, but is not deemed to be persuasive for the following reasons. Hu et al. teach that their study has two implications. First, a careful hunt for corroborating evidence of a role in breast cancer should precede any further study of genes with less than 5-fold expression level change. Second, any genes with 10-fold changes or more are likely to related to breast cancer and warrant attention

(2nd paragraph of left column of page 412). Hu et al. teach that it is likely that this threshold will change depending on the disease as well as the experiment (2nd paragraph of left column of page 412). These teachings caution researchers from drawing conclusions based upon small changes in transcription levels between normal and cancerous tissue. Hu et al. clearly states: "it is not uncommon to see expression changes in microarray experiment as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful" (bottom of right column of page 411). Hu et al. further states: "in any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study" (1st paragraph of left column of page 405).

Accordingly, in view of the limited disclosure in the instant case—lack of disclosure of the "cut-off ratio" that was used to determine whether a hybridization signal was significant, lack of the statistical analysis, lack of the validation of universal normal control, and lack of establishment of a correlative link between gene expression and protein level or a causal link between gene expression and colon, lung or prostate tumours, the teachings of Hu et al. support the Examiner's position that further research is needed to reasonably identify or confirm a specific and substantial utility for the instantly claimed polypeptide of SEQ ID NO: 14 and its variants.

Beginning at the 2nd paragraph of page 21 of the Brief, Appellant argues that it is more likely than not for increased mRNA levels to predict increased protein levels. Appellant presents a declaration by Dr. Polakis under 37 CFR 1.132 as evidence that mRNA expression correlates well with protein levels in general. Appellant submits that while the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Dr. Polakis declaration greatly exceed this legal standard. In the declaration, Dr. Polakis states that a primary focus of the tumor antigen project is to identify tumor cell markers useful as targets for diagnosis and treatment of cancer in humans. Dr. Polakis states that a variety of scientific techniques, including microarray analysis, have been used for detecting and studying differential gene expression in human tumor cells relative to normal cells at genomic DNA, mRNA, and protein levels. Dr. Polakis states that approximately 200 genes transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states antibodies to about 30 of the tumor antigen proteins have been developed and used to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Dr. Polakis states approximately 80% samples show correlation between increased mRNA levels and changes in the level of protein expressed from that mRNA. Dr. Polakis states that it remains a central dogma in molecular biology that increased RNA levels are predictive of corresponding increased levels of the encoded protein. Dr.

Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule.

The declaration of Dr. Polakis is insufficient to overcome the rejection of claims 72-79 and 82-84 under 35 U.S.C.§101 and Appellant's argument is not deemed to be persuasive for the following reasons. First of all, it is important to note that Dr. Polakis clearly states that a variety of scientific techniques, including microarray analysis, have been used for detecting and studying differential gene expression in human tumor cells relative to normal cells at genomic DNA, mRNA, and protein levels. Dr. Polakis does not state that microarray analysis *alone* can establish the use of a polypeptide as a diagnostic marker for a specific tumor. In fact, the art teaches the results obtained from microarray analysis require confirmation by independent methods, such as northern blot analysis and Western blot analysis (see, e.g., Wary et al., Molecular Cancer 2:25, 2003; Yang et al., Arterioscler Thromb Vasc Biol 22:1797-1803, 2002). Secondly, Dr. Polakis states approximately 80% samples show correlation between increased mRNA levels and *changes in the level of protein* expressed from that mRNA. However, Dr. Polakis does not state whether the increase in protein level was significant enough to be meaningful as being a diagnostic marker for colon, lung or prostate tumors.

Thirdly, Dr. Polakis states that approximately 200 genes transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis does not state that how many proteins encoded by the 200 genes are

expressed at significantly higher levels than in corresponding normal human cells. Dr. Polakis states antibodies to about 30 of the tumor antigen proteins have been developed and used to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Dr. Polakis does not state that the 30 of "tumor antigen proteins" are expressed at significantly higher levels than in corresponding normal human cells.

Moreover, the declaration does not provide data such that the Examiner can independently analyze and draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoding polypeptide. In fact, the art teaches the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (Haynes et al., Electrophoresis, 19:1862-1871, 1998; see, left column of page 1863; Figure 1). While the absolute certainty is not the legal standard for utility, a specific and substantial utility in reasonably confirmed and practical form is required for the claimed invention.

Furthermore, the specification provides no information regarding the specific degrees of the increase in mRNA level or protein levels of PRO1866 in tumor tissues relative to corresponding normal tissues. There is no statistical analysis of the expression data. For example, there is no disclosure of the number of tumor samples and control

samples that were analyzed, which is clearly required for the establishment of a reliable diagnostic marker for colon, lung or prostate tumors. The specification merely discloses that if the hybridization signal of a probe from a test (disease tissue) sample is greater than hybridization signal of probe from control (normal tissue) sample, the gene(or genes overexpressed in the disease are identified (lines 22-24 of page 134). The art cautions researchers from drawing conclusions based upon small changes in transcription levels between normal and cancerous tissue, as noted above.

Beginning at the bottom of page 22 of the Brief, Appellant argues that the Examiner has also misunderstood the teachings in Wary et al. and Yang et al. and therefore has reached an incorrect conclusion that the art teaches that results obtained from microarray analysis require confirmation by independent methods. Appellant submits that Wary et al. and Yang et al. simply further tested the protein or mRNA expression of the identified genes in the microarray analysis with other techniques available in the art, such as Northern blot and Western blot.

Appellant's argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, the examiner's position is in agreement with the declaration of Dr. Polakis et al., who clearly state that a variety of scientific techniques, including microarray analysis, have been used for detecting and studying differential gene expression in human tumor cells relative to normal cells at genomic DNA, mRNA, and protein levels. Dr. Polakis does not state that microarray analysis alone can establish

the use of a polypeptide as a diagnostic marker for a specific tumor. Secondly, the cited art explicitly teaches that results obtained from microarray analysis require confirmation by independent methods. For example, at 2nd paragraph of right column of page 1799, Yang et al. clearly states, "To validate the gene expression data by a second, more sensitive, quantitative, and independent method, we analyzed the expression of 12 of the identified genes...". In another cited publication (Journal of Proteome Research, 2:405-412, 2003), Hu et al. teach "in any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study" (1st paragraph of left column of page 405). There would be no logical rational for authors of the cited papers to perform additional assays if microarray alone can reasonably identify or confirm the use of a polypeptide or a nucleic acid as a diagnostic marker for a specific tumor or a therapeutic target.

Beginning at the 3rd paragraph of page 23 of the Brief, Appellant criticizes examiner's analysis of Declaration of Dr. Polakis and argues that Dr. Polakis's declaration is not merely conclusive and the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art. Appellant further submits that this rejection is improper under both the case law and the utility guidelines. Appellant' argument has been fully considered, but is not deemed to be persuasive for the reasons set forth above.

Beginning at page 25 of the Brief, Appellant presents a declaration from Dr. Smith as the evidence that the universal normal control is a well-accepted, informative, and reliable control. Dr. Smith states that molecules identified as being detectably overexpressed in a human tumor of epithelial origin as compared to the universal normal control sample are useful as diagnostic markers for the determination of the presence of that particular type of human tumor.

The declaration by Dr. Smith is insufficient to overcome the rejection of claims 72-79 and 82-84 under 35 U.S.C. §101 for the following reasons. First of all, the declaration does not provide evidence or data such that the Examiner can independently analyze and draw conclusions. Only Dr. Smith's opinions are provided in the declaration. There is no evidentiary support to Dr. Smith's statement that molecules identified as being detectably overexpressed in a human tumor of epithelial origin as compared to the universal normal control sample are useful as diagnostic markers for the determination of the presence of that particular type of human tumor. There is no art support for Appellant's assertion that the universal normal control is a well-accepted, informative, and reliable control.

Dr. Smith states: "Microarray analysis performed in my laboratory have confirmed the general *correlation* in overall gene expression profiles between (i) the universal normal control sample and (ii) individual normal non-cancerous human tissue samples of epithelial origin". However, such a statement does not indicate how well the universal

control reflects the actual gene expression level in each of pooled tissues. How many normal human tissues samples of epithelial origin were pooled? How were the normal control samples pooled? What were the expression levels in each of pooled normal tissues? The fact that the pooled normal control samples were used implies, by itself, variation of the gene expression levels in each of pooled normal tissues; otherwise, if the gene expression levels in all normal control tissues of epithelial origin were identical or very similar, there would no need to use the pooled universal control. Unfortunately, the declaration of Dr. Smith does not provide any information or evidence that could be used to address any of these issues.

Dr. Smith states: "microarray analysis actually performed in my laboratory have shown that when molecules are identified as being overexpressed in a human tumor sample of epithelial origin relative to the universal normal control sample, in a majority of cases, that molecule is also confirmed as being overexpressed in the human tumor tissue sample relative to its normal human tissue counterpart". However, Dr. Smith does not say how "a majority of cases" is defined. Does the "majority" mean 50.1% of all cases or 99% of all cases? If 99% of all cases were confirmed, the nucleic acid would *likely* to have a specific and substantial utility as a diagnostic marker for a certain tumor; on the other hand, if only 50.1% of all cases were confirmed, the utility of the nucleic acid is not substantial. After all, Dr. Smith's declaration shows that the microarray cannot rule out the false positive results and the results based upon microarray analysis need to be confirmed.

Moreover, the declaration by Dr. Smith addresses one specific issue, the normal tissue control; it does not establish the use of the PRO1866 polypeptide as a diagnostic marker for colon, lung or prostate tumors. Even if the universal normal control were a well-accepted, informative, and reliable control, the limited disclosure would still not be found to provide a specific and substantial utility for the polypeptide of SEQ ID NO: 14 and its variants for the reasons set forth at pages 16-19 above. Thus, the utility rejection must be held.

At the top of page 28 of the Brief, Appellant concludes this section by stating that the instant specification discloses a specific, credible and substantial utility for the PRO1866 polypeptide as a diagnostic marker for colon, lung or prostate tumors. The Examiner believes that the rejections should be sustained for the reasons set forth above.

II. Rejection of claims 72-79 and 82-84 under 35 USC § 112, 1st paragraph, enablement

Claims 72-79 and 82-84 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Appellant refers to the arguments and information presented in response to the rejection under 35 U.S.C. § 101. Appellant submits that the PRO1866 polypeptides have utility in

the diagnosis of cancer. The Examiner believes that the rejection should be sustained for the reasons set forth above.

Beginning at the bottom of page 28 of the Brief, Appellant responds to the issue related to the scope of enablement, which is set forth on the assumption that the claimed invention has a specific and substantial utility. Appellant argues that the claimed variants all share the functional limitation that "the nucleic acid encoding said polypeptide is overexpressed in colon, lung, or prostate tumor cells" and Example 30 of the present application provides a step-by-step guidelines and protocols for microarrays. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO1866 protein is overexpressed in colon, lung or prostate tumor cells, and therefore falls within the parameters of the claimed invention. Appellant further submit that the specification describes methods for the determination of percent identity between two amino acid sequences and provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity. Appellant submits that one of ordinary skill in the art has a sufficient high level of technical competence to identify sequences with at least 80% identity to SEQ ID NO: 14.

Appellant' argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, while the claims recite a limitation "wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells", such

a limitation does not limit the scope of the invention in actuality because the specification does not reasonably identify or confirm that the polypeptide or the nucleic acid encoding the polypeptide is overexpressed in colon, lung or prostate tumor cells. Secondly, the microarray analysis disclosed in Example 30 merely measures the mRNA level, does not measure the level of a polypeptide, as noted above. Thirdly, a method of calculating the percentage identity is not equivalent to a method of making and it does not provide sufficient guidance on how to make the functional variants of the polypeptide of SEQ ID NO: 14.

Furthermore, Appellant's argument that the specification provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity is simply incorrect. The functional activity recited in the instant claims is "wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung, or prostate tumor cells". Nowhere does the specification provide guidance as to changes that may be made to a PRO polypeptide without adversely affecting such a recited activity. Procedures for making variants of SEQ ID NO: 14 which have at least 80% identity to SEQ ID NO: 14 and retains its recited activity are not conventional in the prior art because the prior art does not teach that it is predictable that a variant of polypeptide or a nucleic acid will be necessarily overexpressed if a single polypeptide or nucleic acid is overexpressed in a certain type of tumor as compared with a normal control, such as colon, lung or prostate tumors.

Accordingly, even if the polypeptide of SEQ ID NO: 14 were to have a patentable utility, the instant disclosure would not be found to be enabling for the genus of polypeptides encompassed by the instant claims. It would require undue experimentation for one skilled in the art to make and use the claimed invention commensurate in scope with the claims.

At the 2nd paragraph of page 30 of the Brief, Appellant argues that a considerable amount of experimentation is permissible, if it is merely routine. Appellants further submits that the identification of variant PRO1866 polypeptides having 80% identity to SEQ ID NO: 14, wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells, can be performed by techniques that were well known in the art, and that the performance of such work does not require undue experimentation. Appellant' argument has been fully considered, but is not deemed to be persuasive for the reasons set forth immediately above.

At the 3rd paragraph of page 30 of the Brief, Appellant concludes this section by urging that the rejection of claims 72-79 and 82-84 under 35 U.S.C. § 112, first paragraph be reversed. The Examiner believes that the rejections should be sustained for the reasons set forth above.

III. Rejection of claims 72-76, 83, and 84 under 35 USC § 112, 1st paragraph, written description

Claims 72-76, 83, and 84 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Beginning at page 31 of the Brief, Appellant, citing case law, reviews the legal standard for written description, with which the Examiner takes no issue.

At the 2nd paragraph of page 32 of the Brief, Appellant submits that the instant specification evidences the actual reduction to practice of the amino acid sequence of SEQ ID NO: 14. Thus, the genus of the polypeptides with at least 80% sequence identity to SEQ ID NO: 14, whose encoding nucleic acids possess the functional property of being overexpressed in colon, lung or prostate tumor cells, would meet the requirement of 35 U.S.C.§ 112, first paragraph as providing adequate written description.

Appellant' argument has been fully considered, but is not deemed to be persuasive for the following reasons. While the specification provides an adequate written description for the PRO1866 polypeptide of SEQ ID NO: 14 (and its mature form, i.e., lacking the signal peptide sequence), it fails to provide adequate written description for its variants or homologues because the polypeptide of SEQ ID NO: 14 is not representative species of the claimed genus. The recited functional limitation, "wherein the nucleic acid

encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells", does not limit the scope of the invention because the specification does not provide sufficient evidence showing that the polypeptide of SEQ ID NO: 14, let alone its variants, is overexpressed in colon, lung or prostate tumor cells and can be used as a reliable diagnostic marker for colon, lung or prostate tumors. As noted in the utility rejection section, the cited prior art also teaches against the likelihood that the single species of SEQ ID NO: 14 is reduced to practice by disclosing its complete structure. Therefore, the instant disclosure fails to evidence the actual reduction to practice of the amino acid sequence of SEQ ID NO: 14, let alone its variants.

From the 3rd paragraph of page 32 of the Brief, Appellant disagrees with the Examiner's opinion that only one polypeptide sequence has been identified with a potential link to cancer as recited in the claims. Appellant submits that the inventor is not required to describe every single detail of his invention. Appellant further argues that the present invention is from the field of recombinant DNA technology, it is well established that the level of skill in this field is relatively high and the teachings imparted in the specification must be evaluated through the eyes of a highly skilled in the artisan as of the date the invention was made.

Appellant' argument has been fully considered, but is not deemed to be persuasive for the following reasons. The Examiner agrees that compliance with the written description requirement does not require that the inventor describe every single detail of his

invention. However, the description has to satisfy the description requirement by, for example, providing representative species of the claimed genus or the structural and functional characteristic of the claimed genus. In the instant case, the specification merely discloses a single species, the polypeptide of SEQ ID NO: 14, fails to disclose any specific biological functions or any physiological significance of the claimed genus, and fails to disclose the conserved regions that are critical to the functions of the claimed genus and methods of making the claimed genus of variants of the polypeptide of SEQ ID NO: 14. The specification does not provide sufficient evidence showing that the polypeptide of SEQ ID NO: 14 and its variants are overexpressed in colon, lung or prostate tumor cells, as noted in the utility rejection section.

While the level of skill in the DNA recombination technology is relatively high, the microarray analysis has been widely used to determine the gene expression levels as demonstrated by the cited publications, the art does not teach that if a single polypeptide or a nucleic acid is overexpressed in a certain type of tumor as compared with a normal control, such as colon, lung or prostate tumors, variants of the polypeptide or nucleic acid will necessarily be overexpressed in the tumor.

At the 1st paragraph of page 33 of the Brief, Appellant submits that Example 30 of the present application provides a step-by-step guidelines and protocols for microarrays. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO1866 protein or its mRNA is overexpressed in colon, lung or prostate

tumor cells, and therefore falls within the parameters of the claimed invention. Appellant further submit that the specification describes methods for the determination of percent identity between two amino acid sequences and provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity.

Appellant' argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, the microarray analysis disclosed in Example 30 merely measures the mRNA level, does not measure the level of a polypeptide, as noted above. Second, a method of calculating the percentage identity is not equivalent to a method of making and it does not provide description for the instantly genus of PRO1866 polypeptide variants. Moreover, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In the instant case, only one polypeptide sequence has been identified with a potential link to colon, lung or prostate tumors. No other species have been disclosed. One species is not adequately representative of the many sequences encompassed by the claims.

Furthermore, Appellant's argument that the specification provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity is simply incorrect. The functional activity recited in the instant claims is "wherein

the nucleic acid encoding said polypeptide is overexpressed in colon, lung, or prostate tumor cells". Nowhere does the specification provide guidance as to changes that may be made to a PRO polypeptide without adversely affecting such a recited activity. Procedures for making variants of SEQ ID NO: 14 which have at least 80% identity to SEQ ID NO: 14 and retains its activity are not conventional in the art because the prior art does not teach that if a single polypeptide or nucleic acid is overexpressed in a certain type of tumor as compared with a normal control, such as colon, lung or prostate tumors, its variants will necessarily be overexpressed.

At the 2nd paragraph of page 33 of the Brief, Appellant argues that Appellants have recited structural features, namely 80% sequence identity to SEQ ID NO: 14, which are common to the genus. Appellant also argues that appellant has also provided guidance as to how to make the recited variants of SEQ ID NO: 14, including listings of exemplary and preferred sequence substitutions. The genus of claimed polypeptides is further defined by having a specific functional activity for the encoding nucleic acids.

Appellant' argument has been fully considered, but is not deemed to be persuasive for the reasons set forth above. Moreover, the recited sequence percent identity does not represent an effective structural limitation because it says nothing about the conserved structure or the distinguishing feature of the genus, or the relation of structure to function.

From the bottom of page 33 the Brief, Appellant concludes this section by urging that the rejection of claims72-76, 83, and 84 under 35 U.S.C. § 112, first paragraph for written description be reversed. The Examiner believes that the rejections should be sustained for the reasons set forth above.

IV. Rejection of claims 72-75, 83, and 84 under 35 USC § 102 (e)

Claims 72-74, 83, and 84 are rejected under 35 U.S.C. 102(e) as being anticipated by Young et al. (U.S. Patent No. 6,525,174 B1, Feb. 25, 2003; filing date: Dec. 4, 1998).

Claims 72-75, 83, and 84 are rejected under 35 U.S.C. 102(e) as being anticipated by Stanton et al. (U.S. 2002/0110804 A1, Aug. 15, 2002; 102 (e) date: March 31, 2000).

At the middle of page 34 of the Brief, Appellant argues that the references are not prior art, as demonstrated by the declaration under 37 C.F.R. §1.131 of all the inventors.

Appellant' argument has been fully considered, but is not deemed to be persuasive and the declaration filed under 37 C.F.R. 1.131 by the inventors Goddard et al. has been considered but is ineffective to overcome the references U.S.Patent No. 6,525,174 and US2002/0110804A1 because the scope of the declaration is not commensurate with the scope of the claims. The instant claims encompass a genus of isolated polypeptides comprising the polypeptide of SEQ ID NO: 14 or its variants. Each of the cited 102 (e) references teach a species of the polypeptide of SEQ ID NO: 14. While the declaration establishes the showing of possession of the polypeptide of SEQ ID NO: 14 and the

nucleic acid sequence of SEQ ID NO: 13, it does not show that Appellant was in possession of the species taught by Young et al. or by Stanton et al. prior to the effective filing date of U.S. Patent No. 6,525,174 or U. S. patent application publication US2002/0110804A1.

Beginning at the middle of page 35 of the Brief, Appellant, citing MPEP and case law, argues that the declaration under 37 C.F.R. §1.131 demonstrates possession of the claimed genus prior to the reference dates. Appellant submits that as described above under Issue III, the disclosed polypeptide of SEQ ID NO: 14 is representative for a genus encompassing its variants.

Appellant' argument has been fully considered, but is not deemed to be persuasive for the reasons set forth at Section III (Rejection of claims 72-76, 83, and 84 under 35 USC § 112, 1st paragraph, written description). It is points out that Appellant was not in possession of the claimed genus of polypeptides at the actual filing date of the instant application, nor before the filing dates of U.S. Patent Application Publication No. 2002/0110804 A1.

At the middle of page 36 of the Brief, Appellant cites the Example 14 of the Written Description Guidelines of the U.S. Patent Office and argues that the claimed polypeptide variants meet the standards set forth in the written description guidelines, standards that demonstrate that Appellants had possession of the claimed genus.

Appellant argues that the declaration demonstrates that Appellant had cloned and sequenced the nucleic acid encoding SEQ ID NO: 14 prior to March 31, 2000. Procedures for making the claimed variant proteins were well known in the art before March 31, 2000. The microarray assay for detecting the recited functional activity of the nucleic acids encoding the claimed polypeptide variants was also known in the art, and as demonstrate by Exhibit B of the declaration. Appellant further submits that the claimed genus of variants possess both the specified functional activity for the encoding nucleic acid, and a defined degree of sequence identity to the SEQ ID NO: 14.

Appellant' argument has been fully considered, but is not deemed to be persuasive for the reasons set forth at Section III (Rejection of claims 72-76, 83, and 84 under 35 USC § 112, 1st paragraph, written description). Moreover, in Example 14 of the Written Description Guidelines of the U. S. Patent Office, the specification exemplifies that a protein of SEQ ID NO: 3 isolated from liver catalyzes the reaction of A→B, and the procedures for making variants of SEQ ID NO: 3 that have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art because deletions, substitutions, insertions, and additions of uncritical amino acid residues would not affect the enzyme activity. Moreover, such an enzyme would have a conserved structure that is responsible for the enzyme activity. Thus, it is likely predictable, based upon percent identity, which variant would share the same function. In contrast, in the instant case the percentage identity is 80%, which is much lower than 95% recited in the Example 14; the recited limitation, "wherein the nucleic acid encoding said polypeptide is

overexpressed in colon, lung or prostate tumor cells", is not sufficiently supported by the specification as noted above; procedures for making variants of SEQ ID NO: 14 which have at least 80% identity to SEQ ID NO: 14 and retains its activity are not conventional in the art because the prior art does not teach that if a single polypeptide or nucleic acid is overexpressed in a certain type of tumor as compared with a normal control, such as colon, lung or prostate tumors, its variants will necessarily be overexpressed.

At the middle of page 37 of the Brief, Appellant argues that the declaration demonstrates that Appellant had cloned and sequenced the nucleic acid encoding SEQ ID NO: 14 prior to December 4, 1998. Procedures for making the claimed variant proteins were well known in the art before December 4, 1998. Appellant submits that the evidence provided in the declaration, together with what was known in the art at the time, suffices to demonstrate that Appellant had possession of the claimed genus including the polypeptide of Young et al. before the December 4, 1998 priority date of Young et al. Appellant' argument has been fully considered, but is not deemed to be persuasive for the reasons set forth immediately above.

At the bottom of page 37 of the Brief, Appellant concludes this section by urging the reversal of the rejections of the claims as anticipated by Young et al. or Stanton et al. under 35 U.S.C. § 102 (e). The Examiner believes that the rejections should be sustained for the reasons set forth above.

At the top of page 38 of the Brief, Appellant concludes their argument by urging reversal of all the outstanding rejections of claims 72-79 and 82-84. The Examiner believes that the rejections should be sustained for the reasons set forth above.

Therefore, for reasons set forth above, Appellant's arguments and evidence have been fully and carefully considered, but are not considered sufficient to rebut the prima facie case of lack of utility, enablement and written description.

For the above reasons, it is believed that the rejection should be sustained.

Respectfully submitted

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Ruixiang Li, Ph.D.
Primary Examiner
October 24, 2005

Conferees
Anthony Caputa, Ph.D.
SPE, Art Unit 1646

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Yvonne Eyler, Ph.D.
SPE, TC1600